PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:
Mewburn Ellis
York House
23 Kingsway
London

WC2B 6HP

RECEIVED
- 3 AUG 2001

COPY

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing *(day/month/year)* 02 AUG 2001

Applicant's or agents's file reference
GPSBP5944723

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB01/03403	30/07/2001	28/07/2000

Applicant
Euroflow (UK) Limited et al

Title of the invention
Chromatography Methods and Chromatography Apparatus

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

☒ was transmitted to the International Bureau on 02 AUG 2001 02-08-2001

☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:

☐ because the necessary national security clearance has not yet been obtained.

☐ because *(reason to be specified)*:

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the receiving Office	Authorized officer
The Patent Office Cardiff Road, Newport South Wales NP10 8QQ	Melanie Williams
Facsimile No.	Telephone No. 01633 814383

Form PCT/RO/105 (July 1992)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
STONER, G., Patrick
Mewburn Ellis
York House
23 Kingsway
London, Greater London WC2B 6HP
ROYAUME-UNI

RECEIVED
15 FEB 2002

Date of mailing (day/month/year)	
07 February 2002 (07.02.02)	
Applicant's or agent's file reference	IMPORTANT NOTICE
GPSBP5944723	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB01/03403	30 July 2001 (30.07.01)	28 July 2000 (28.07.00)

Applicant
EUROFLOW (UK) LIMITED et al

1. Notice is hereby given that the International Bureau has **communicated**, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:
   KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AG,AL,AM,AP,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EA,EC,
   EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,
   MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on
   07 February 2002 (07.02.02) under No. WO 02/10739

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and the PCT Applicant's Guide, Volume II.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.91.11

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:
MEWBURN ELLIS
Attn. Stoner, Patrick
York House
23 Kingsway
London WC2B 6HP
UNITED KINGDOM

RECEIVED
21 NOV 2001

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 21/11/2001
Applicant's or agent's file reference GPSBP5944723	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/GB 01/03403	*International filing date (day/month/year)* 30/07/2001
Applicant EUROFLOW (UK) LIMITED et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41–22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Mildred Condron

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
GPSBP5944723		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 01/03403	30/07/2001	28/07/2000
Applicant		
EUROFLOW (UK) LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] *furnished subsequently to this Authority in computer readble form.*

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   METHODS AND APPARATUS FOR PACKING CHROMATOGRAPHY COLUMNS AND CHROMATOGRAPHY COLUMN

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] *the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III.* The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 13

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted]B 01/03403

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N30/56 G01N30/60 B01D15/08 G01F23/296

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N B01D G01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, COMPENDEX, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 061 371 A (TABATA TAKESHI ET AL) 29 October 1991 (1991-10-29) the whole document	1,4,5, 7-9, 11-15, 17-19, 21-32
X	GB 1 312 096 A (ECODYNE CORP) 4 April 1973 (1973-04-04)	1,2,4-6, 17,18, 22,24,29
Y	page 2, line 27-47; figure 1	2,3,27, 28,30
A	US 4 324 131 A (ROSENCWAIG ALLAN) 13 April 1982 (1982-04-13)	1-32
Y	column 2, line 20-47	2,3,27, 28,30

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2001	21/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Müller, T

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/03403

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5061371	A	29-10-1991	NONE		
GB 1312096	A	04-04-1973	BE	759217 A1	30-04-1971
			CA	941984 A1	12-02-1974
			CH	522209 A	15-06-1972
			DE	2057238 A1	24-06-1971
			ES	384863 A1	16-03-1973
			FR	2069813 A5	03-09-1971
			JP	48015143 B	12-05-1973
US 4324131	A	13-04-1982	NONE		

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

STONER, G., Patrick
Mewburn Ellis
York House
23 Kingsway
London, Greater London WC2B 6RP
ROYAUME-UNI

RECEIVED
22 OCT 2001

Date of mailing (day/month/year) 11 October 2001 (11.10.01)	
Applicant's or agent's file reference GPSB/5944723	**IMPORTANT NOTIFICATION**
International application No. PCT/GB01/03403	International filing date (day/month/year) 30 July 2001 (30.07.01)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 28 July 2000 (28.07.00)
Applicant EUROFLOW (UK) LIMITED et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
28 July 2000 (28.07.00)	0018522.3	GB	05 Sept 2001 (05.09.01)
14 May 2001 (14.05.01)	0111785.2	GB	12 Sept 2001 (12.09.01)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Tessadel PAMPLIEGA

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

STONER, G., Patrick
Mewburn Ellis
York House
23 Kingsway
London, Greater London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year) 28 September 2001 (28.09.01)	
Applicant's or agent's file reference GPSBP5944723	**IMPORTANT NOTIFICATION**
International application No. PCT/GB01/03403	International filing date (day/month/year) 30 July 2001 (30.07.01)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 28 July 2000 (28.07.00)
Applicant EUROFLOW (UK) LIMITED et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
28 July 2000 (28.07.00)	0018522.3	GB	05 Sept 2001 (05.09.01)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Somsak THIPHRAKESONE

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

STONER, G., Patrick
Mewburn Ellis
York House
23 Kingsway
London, Greater London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
24 August 2001 (24.08.01)	
Applicant's or agent's file reference	**International application No.**
GPSBP5944723	PCT/GB01/03403

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

EUROFLOW (UK) LIMITED (for all designated States except US)
HOFMANN, Martin,John (for US)

International filing date	:	30 July 2001 (30.07.01)
Priority date(s) claimed	:	28 July 2000 (28.07.00) 14 May 2001 (14.05.01)
Date of receipt of the record copy by the International Bureau	:	14 August 2001 (14.08.01)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,
EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,
LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,
UG,US,UZ,VN,YU,ZA,ZW

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Anman QIU

Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
24 August 2001 (24.08.01)	
Applicant's or agent's file reference	***International application No.***
GPSBP5944723	PCT/GB01/03403

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [ ] *confirmation of precautionary designations*
- [X] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

(12) INTERNATIONAL APPLI[illegible]ON PUBLISHED UNDER THE PATENT CO[illegible]RATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/10739 A1

(51) International Patent Classification[7]: G01N 30/56, 30/60, B01D 15/08, G01F 23/296

(21) International Application Number: PCT/GB01/03403

(22) International Filing Date: 30 July 2001 (30.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0018522.3	28 July 2000 (28.07.2000)	GB
0111785.2	14 May 2001 (14.05.2001)	GB

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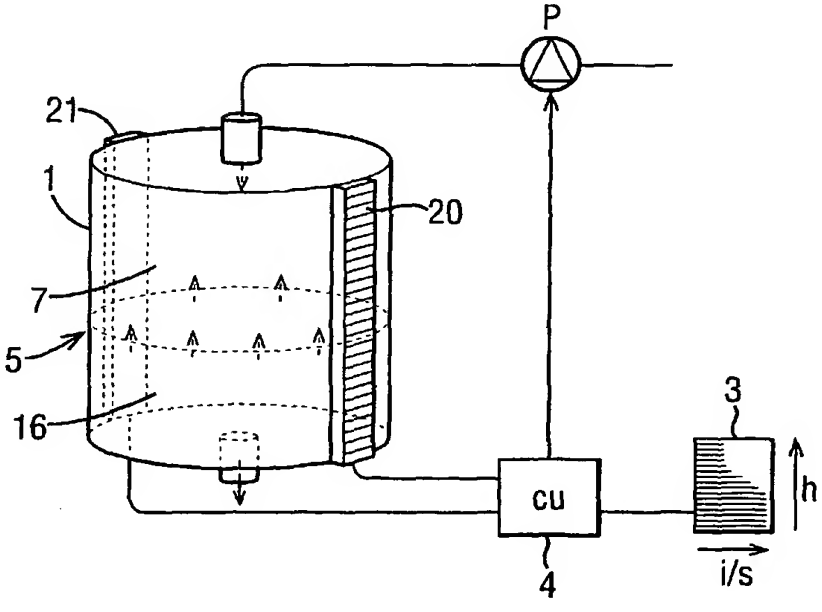
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: METHODS AND APPARATUS FOR PACKING CHROMATOGRAPHY COLUMNS AND CHROMATOGRAPHY COLUMN



(57) Abstract: Ultrasound transceivers (20) are distributed up the side wall of a chromatography column (1) and enable tracking of the progress of a rising bed front (5) during packing. Comparison with a predetermined stored profile is used for feedback control of the packing pump P. Other uses of ultrasound monitoring of the column interior are disclosed.

WO 02/10739 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHODS AND APPARATUS FOR PACKING CHROMATOGRAPHY COLUMNS AND CHROMATOGRAPHY COLUMN

FIELD OF THE INVENTION

This invention has to do with methods and apparatus used in chromatography. The new proposals are concerned with finding out the condition of a bed of a particulate medium in the bed space of a chromatography column. This assessment might be during the packing of the column or afterwards i.e. during or after a chromatography process using the packed bed.

BACKGROUND OF THE INVENTION

The conventional principles and apparatus for packed-bed chromatography are well-established. The present invention is concerned with issues arising in commercial-scale preparative chromatography, where columns are often very large and any one or more of the particulate packing medium, the product to be separated and the time taken up in arranging the running of the procedure is/are of very high value.

It is well known that a packed column has to be continuously, uniformly and entirely filled with the relevant medium under an appropriate degree of compression of its particles.

Conventional column packing, an operation requiring great care and experience, involves removing the top plate or "cell" of the column and pouring in a slurry of

the relevant medium in a liquid carrier. More recently the use of a packing port has become favoured because it obviates taking the lid off. Various kind of valved ports have been proposed for this; see for example GB-A-2258415, WO 96/10451 and WO 99/64130. The column generally has upper and lower restricted-permeability elements - mesh or sinter layers - to retain the media particles, and the packing port provides communication directly into the bed space past i.e. penetrating one or both of these restricted-permeability layers. To pack, typically the column is filled with liquid and the medium slurry pumped in through the packing port at one end, liquid carrier leaving the column via the permeable element at the other. The particulate medium is retained and gradually accumulates until the column is full. The accumulating bed is compressed by the controlled pressure from the pumped liquid and - in the usual case when packing from the top - also by the weight of the upper part of the bed. There is a subtle, continuous variation in the conditions experienced by the medium. A common procedure is for the operator to continue pumping until the column is essentially full, whereupon the pump usually cuts out spontaneously. As the liquid flow pressure is relieved, the packed bed then "relaxes" to fill the column with a more uniform compression profile over its length.

Even with packing ports, the packing of chromatography columns is a skilled job requiring training and experience. A packing nozzle helps to achieve consistent results, but only experience and time-consuming testing of trial packs can indicate the optimal slurry concentrations and pump pressure profiles for a given medium in a given column. Since many columns are of steel the operator can have very little idea of what is happening inside.

SUMMARY OF THE INVENTION

We have found that by transmitting periodic mechanical vibratory signals, in particular sonic or ultrasonic signals, through the bed space of a column, one can obtain useful information about the condition and/or position of a bed of particulate medium in that space by detecting the transmitted signal. We have confirmed that apparatus to implement these findings is practical to make and use, and that useful results are obtained.

One aspect of the invention is to use the detection of a sonic or ultrasonic transmission through the bed space as a means of improving the process of packing the column, by marking the passage of the advancing "front" of the accumulating bed and/or to observe conditions in the body of the bed which may be of practical importance.

Other aspects relate to detecting the properties of

sonic/ultrasonic transmissions through the bed space as a means of noting the presence of other materials in the bed, e.g. components which are eluting through the column, or impurities which may be fixedly bound in the column.

Other aspects are chromatography apparatus adapted for the performance of the various method aspects, comprising one or more sonic/ultrasonic transmitters/detectors.

Further aspects relate to the provision of chromatography packing apparatus enabling a packing procedure to be monitored and to assess its conformity with a predetermined packing profile, and for using automatic or operator-controlled feedback to approximate the actual packing process to the predetermined profile.

Aspects of the invention are set out in the claims.

We have determined that a sonic/ultrasonic transmission through the bed space of a chromatography column is attenuated by the presence of the bed and its speed increased, i.e. its time of flight reduced, compared with when the bed is not present. Either or both of these effects may be used to obtain data about the bed in the column. Also, either or both of these properties (amplitude, speed) can be influenced by the presence of adventitous substances in the bed.

Thus, the present proposals enable any one or more

of

- determining a height to which packing medium has accumulated during packing;

- determining a packing density/degree of compression of packed medium;

- determining - by means of plural transmissions along different paths - a rate of advance of the bed front during packing;

- determining the presence/position/extent of contaminant materials or eluting product components in the bed from time to time, e.g. as chromatography proceeds.

Preferably the state of packing of materials within the chromatography column can be assessed by measuring the time taken between transmission and reception of a transmission, i.e. the speed.

Alternatively or additionally, measuring the attenuation of a transmission can be particularly useful in determining the height of a slurry bed within the chromatography column.

Preferably the transmission is directed through the interior of the column in a direction substantially parallel to a base of the column, e.g. in a substantially radial direction so that the transmission crosses through or close to the axis of the column. The transmission may be focussed by a sonic lens.

The transmission is preferably in a pulsed form. This aids detection.

The frequency of the transmission is selected to obtain a suitable detectable signal for the purpose in hand. Preferred frequencies are ultrasonic, e.g. ≥ 0.5MHz, ≥ 1.0MHz, ≥ 1.5MHz. For example a transmission of 2 MHz was found to give a suitable detectable signal. The attenuation suffered by a 2.5MHz transmission passing through a slurry bed was found to be greater than that at 2MHz.

When measuring the speed of a transmission minimum attenuation may be desired. When determining the height of a slurry bed within the chromatography column it may be desirable to use a sonic transmission which is more significantly attenuated by passing through the slurry bed.

A sonic/ultrasonic transmitter is used to generate the transmission. The transmitter may be attached to a side wall of the chromatography column, preferably on the outside.

The transmitter may be a transceiver which is capable of detecting as well as transmitting sonic transmissions. Preferably the sonic transceiver comprises a piezoelectric material. Preferably the sonic transceiver is used to transmit a sonic transmission and to receive an echo of this transmission. This technology

is known per se e.g. for measuring fluid velocities in pipes.

The time delay of the echo together with the dimensions of the column can be analysed to find the speed of the sonic transmission and thus obtain information about the packing state of the materials therein. The thickness and material of the chromatography column walls can be taken into account as necessary.

Alternatively sonic transmission may be generated by a transmitter and received separately by a receiver. The transmitter and receiver are then preferably on opposite sides of the column.

In the following proposals it is generally possible to use either a sonic transceiver or separate transmitter and receiver.

Preferably the transmitter is attached to the exterior of the side wall of the column. A lens may be placed between the transmitter and the column surface.

Alternatively a transmitter and/or sonic lens may be embedded within the side wall of the chromatography column or even placed within the column.

The transmitter may be placed at any appropriate height. To detect when the slurry bed has reached a given height in the column then one may place a transmitter at this height and to direct the transmission

substantially parallel to the base of the column.

Preferably more than one transmission path is provided, at different parts of the interior of the chromatography column. This enables e.g. spatial profile of the packing state of materials within the column, useful in checking the uniformity of packing.

For example transmission paths may be at different axial heights.

Each transmission path may have a respective transmitter/detector pair, or a single sonic transmitter/detector may change its position e.g. by sliding to different positions on the exterior of the column's side wall.

A further aspect of the present invention is a method of packing a chromatography column involving pumping a slurry of particles into the column, using a sonic transmission to monitor the height of said slurry within the column and stopping the pumping when the desired height of said slurry within the column is monitored.

Preferably the stopping of the pumping is automated. Preferably a switching device takes an input based on the amplitude of the monitored sonic transmission and switches off the pump when said input indicates that the desired height of slurry within the column has been reached.

A further aspect is a method of packing a chromatography column involving using a pump to pump a slurry of particles into the column, using a sonic transmission to monitor the state of packing of said slurry within the column, comparing the state of packing monitored to a desired state of packing and when the monitored state of packing is different from said desired state of packing adjusting the packing parameters so as to achieve the desired state of packing.

This aspect of the invention may be used in combination with the aspects above.

The packing parameters are any adjustable parameters which affect the packing process, for example the pumping pressure (which may be adjusted by altering the pumping speed). It may also be possible to adjust the concentration of slurry being pumped into the chromatography column.

Preferably the packing parameters are adjusted by means of feedback to the packing apparatus (e.g. the pump), said feedback being based upon the desired state of packing and the state of packing monitored by the sonic transmission.

Preferably the feedback is automated by the use of a computer or appropriate electronic circuits, but it may be possible for the method to be implemented manually. The feedback may be automated by use of a I to P

converter which converts an electric current to a desired pumping pressure. The feedback may be proportional to the difference between the desired state of packing and the state of packing monitored.

Preferably the comparison between the state of packing monitored and the desired state of packing is achieved by comparing the measured speed of the sonic transmission with a desired value for this speed.

Preferably this comparison is carried out continuously during the packing process and continuous feedback to the packing apparatus is generated on the basis of this comparison.

The feedback may enable an increase or decrease in the pumping pressure. For example if the speed of the sonic transmission is lower than the desired value then the density of the slurry is too low and the pumping pressure will need to be increased so as to increase the packing compression and density of the slurry. Equally if the speed of the sonic transmission is higher than the desired value then the packing compression is too high and the pumping pressure will need to be decreased.

Preferably information relating to the desired state of packing is provided in the form of a packing profile which details the transmission properties at various stages during the packing process. These stages may be various points in time since the packing process started.

They may be defined by the duration of time for which the pump has been active, a height in the column which the slurry has reached or a volume of slurry which has been pumped.

The packing profile may for example give a profile of the desired speed of the transmission against a time from the start of the packing process.

It is envisaged that the profile may be derived from measurements carried out during a successful trial packing of a chromatography column.

The profile may give a range of acceptable values, rather than an exact value, for the property e.g. speed of the transmission at each stage during the packing process.

The profiles may differ for different combinations of chromatography column type and slurry type. Therefore it is envisaged that a different packing profile may be provided for each such combination.

The packing profile is also expected to vary according to the path of the transmission in the chromatography column.

Preferably the packing parameters are adjusted on the basis of the packing state monitored by respective ones of plural transmissions and the desired packing state for each respective transmission.

A further aspect of the present invention is a

system for packing a chromatography column, the system comprising a pump for pumping particulate slurry into the column, signal generating means for generating a signal to control a sonic/ultrasonic transmitter, receiving means for receiving a signal from a corresponding receiver, analysing means for analysing a signal received by the receiving means and outputting a result based on analysis of said received signal and pump controlling means for controlling said pump on the basis of the output from said analysing means.

Preferably the system has data means for storing or for reading packing profile data. Preferably said packing profile data contains chromatography column dimension data.

Preferably the analysing means is capable of detecting a signal received by the receiving means which corresponds to a signal previously generated by the signal generating means, calculating the time delay between the generation and detection of said signal, analysing said time delay along with chromatography column dimension data and thus computing the speed of a sonic transmission corresponding to said generated and detected signal and generating an output based on said computed speed of said sonic transmission.

Alternatively or additionally the analysing means is capable of detecting a signal received by the receiving

means which corresponds to a signal previously generated by the signal generating means and generating an output based on the amplitude of said received signal.

Preferably the packing profile data also contains data relating to the type of slurry with which the chromatography column is to be packed. Preferably the packing profile data contains data relating to the desired output from the analysing means during the packing process. Preferably the packing profile data contains data relating to the desired speed of said sonic transmission corresponding to said generated and detected signal.

Preferably the pump control means is capable of controlling the pump on the on the basis of said packing profile data and said outputted result from said analysing means.

Preferably the pump control means is configured to increase the pumping pressure if the result from the analysing means indicates that the velocity of the sonic transmission is lower than desired and to decrease the pumping pressure if the result from the analysing means indicates that the speed of the sonic transmission higher than desired.

It is envisaged that the packing profile data relating to said desired output will detail the desired temporal profile of the output from the analysing means

during the packing process.

It is envisaged that it will be possible to provide the packing profile data on a portable data device such as a smart card or a floppy disk.

Preferably the system for packing the chromatography column is capable of taking inputs from a plurality of receivers/detectors. It is envisaged that each may be located at a different height on the chromatography column.

Preferably the system has a plurality of analysing means, each respective analysing means for analysing a signal from a respective receiving means and generating a result based upon said analysis. Alternatively the system may have an analysing means capable of analysing a plurality of signals received by a plurality of receiving means and capable of generating an output or a plurality of outputs based on analysis of said received signals. Preferably the pump control means is capable of receiving a plurality of outputs from one or more analysing means and controlling said pump on the basis of said outputs.

A further aspect of the present invention is a chromatography column with an attached sonic transmitter or transceiver for transmitting a sonic transmission into the interior of the chromatography column.

A further aspect in the present application has to do with packing a chromatography column. In our work we

have found that although a sonic transmission can be affected by the packing density and pack quality of a bed, these effects are more difficult to detect reliably than the simple large effect on the transmission due to the presence, as opposed to the absence, of the bed (settled or packed media). The latter is a strong change and easily detected, so that the position of the bed "front" can be determined with confidence using such sonic transmissions, even when (as is strongly preferred) the sonic transmitters/receivers are outside the column interior and must act via the column wall. At the same time we have made a new and useful finding that the rate of advance of the bed front during packing is a significant parameter correlating with the quality - in particular the quality in terms of plate value i.e. chromatographic efficiency - of the resulting pack. This is of practical importance because of the difficulty of standardising pack control parameters. For practical reasons the conventional primary control parameter is the packing pressure applied by the pump at the packing port, and packing operatives are accustomed to adjusting this packing pressure during the procedure to achieve desired results. However the absolute values and profiles of the packing pressure for packing a given medium into a given column cannot usefully be prescribed. This is because different column set-ups, even with essentially identical

columns and media, generate significantly different back-pressures associated with variations in slurry concentration, bed support type, buffer viscosity, temperature, column expansion and the flow systems downstream of the bed, e.g. length, diameter and the number and acuity of bends in pipe work. In practice, several trial packs followed by plate value assessments are needed before an optimum packing pressure profile can be settled on for a given column set-up.

A constant packing pressure is not a useful control. In general the flow will be found too high in the early stages. Conversely if fluid flow is held constant the pressure at the end of the procedure is too high for good results. These subtleties are peculiar to closed-column, injected slurry techniques; they do not arise in the conventional open-column pack where essentially all the medium needed for the pack is present in or above the column space at the outset.

Thus we propose a method of packing a chromatography column in which the rate of advance for the bed front is measured and one or more packing parameters -typically pump speed and/or slurry concentration - controlled in dependence on the measurement to approximate the ongoing rate of advance to a target value, or to keep it in or bring it into a target range.

In line with the aspects above, the preferred method

of measuring the rate of advance of the bed front is by detecting successive positions of the bed front using sonic/ultrasonic transmissions through the column interior.

Typically the preferred (target) rate of bed front advance will vary during the pack. The method may involve measuring that rate at plural positions distributed axially (i.e. in the direction of accumulation of the bed) along the column. Control feedback can be arranged by means of conventional processing technology, feeding the output from the relevant sensors, e.g. ultrasound receivers to a control processor for calculation of the real-time rate of advance, comparison with a target value representative of a desired rate of advance or "profile" (variation with time, or with axial location) of the rate of advance, and control signals sent to a pump to determine or vary the rate of pumping accordingly.

Because this method takes direct account of the actual accumulation of the bed, it can avoid some of the trial and error preparation which (for reasons explained previously) is associated with control via monitoring the packing pressure.

While the optimum advance rates and advance rate variation patterns can be determined previously for given columns, liquid and media, it can be said in general that

a preferred "rate of advance" profile will usually have a first phase, corresponding to an initial build-up of medium on the bed support (mesh or sinter), which is slow by comparison with a subsequent main phase which is faster. There may be a gradual increase between the two. This appears in general to lead to better packing results. The difference if any between the rates of advance during the main phase of packing and at the final phase of packing (where the bed approaches the top permeable retainer e.g. mesh or sinter) appears to be less critical. It may be of importance with some media in which case the target profile can be determined accordingly. People packing similar media into similar columns subsequently can then get the benefit of that initial empirical investigation on an automated basis.

A skilled person will appreciate that for the present purposes it may be preferable to have an essentially progressive assessment of the rate of advance of the media front up most or all of the axial extent of the column interior. To this end a series or array of sonic transmission and detection elements e.g. piezoelectric elements may be installed on the chromatography column, preferably on the outside of its the wall so as not to affect the uniformity of the interior. The direction of transmission of the signals from transmitter to receiver is preferably substantially

transverse to the direction of advance of the bed front, since this maximises the difference in effect of the transmission in front of and behind the front. However, other dispositions of sensors and transmitters may be acceptable. For example, an emitter or receiver may be positioned at the end of the column opposite to the end where the bed initially accumulates. It may transmit to or receive from sensors or transmitters disposed on the side of the column. Or, such an arrangement may be combined with a transverse (radial) system; the two systems may reference one another for reliability. And/or, the rate of advance of the bed front may be determined by directing a transmission axially or with an axial component, onto the bed front and detecting the back-reflection from the front. In the latter respect, we note that the use of ultrasonic transceivers to determine the levels of materials in industrial vessels is established practice. Indeed, it has been used in the specialised context of a fluidised bed chromatography column as a means of measuring the height of the particle bed in use. However, these transceivers project laterally inside the column which is acceptable in liquid-containing vessels, and in fluidised bed chromatography processes which are exceptional in that the medium does not fill the column in use, but is not good practice in packed chromatography bed procedures.

Also, the prior art uses of ultrasound transceivers in vessels have not been used to control the rate of advance of a bed front on a feedback basis. There has not previously been any perceived reason for doing so.

The sonic/ultrasonic transmission apparatus may have separate emitters and receivers, or transceivers which combine the two functions. These technologies are in themselves well known, as are arrangements for positioning sonic emitters and receivers effectively on the outside of the vessels so that they will work through the wall. The latter technology is well established in ultrasonic meters which measure fluid flow rates in pipes using Doppler-type effects.

Apparatus for carrying out the method is a further aspect of the invention. In particular the apparatus may comprise a chromatography column adapted with suitable sensors and control circuitry operatively connected to a packing pump to carry out a method as described. A particular apparatus may include an array of sonic sensors/transmitters mounted on (or adapted to be mounted on) a column wall and connected to electronic processing means programmed to determine a rate of advance on the basis of signals from these sensors, compare the rate of advance with desired targets or ranges and, in dependence on the result of the comparison, send or adjust control signals to a packing pump.

A further aspect of the invention is based on a further new finding we have made, which is that the presence of adventitious substances in a packed bed can affect the speed and/or attenuation of sonic transmissions through the bed. It is therefore possible to use such sonic transmission to detect the presence and/or the movement in the bed of such materials. In one aspect such materials might be contained in bands gradually eluting through the bed during a chromatographic process. Using one or more sensor arrangements to detect the passage of such a band at one or more corresponding regions of the column enables a "tracking" of the process which can be helpful to the operator in monitoring the procedure and collecting the separated substances as they emerge. With sufficient sensors, e.g. a series or array as discussed above, the movement of a band of substance through the column can be tracked, and if desired visualised on a display outside the column.

Another use of this finding is as follows. In some processes the materials presented to the column for separation include materials which will bind irreversibly to the chromatographic medium in the column. Generally these bind to the medium immediately or soon after entering the bed. Their permanent binding reduces the transitory binding capacity of the medium which is the

foundation of the chromatographic process for the other components of the mixture. A region in which the bed is progressively less and less effective grows gradually adjacent that end of the column at which the starting material is introduced. In practice there comes a point at which the affected band at the end of the bed is so large that the bed as a whole is inadequate. This usually becomes apparent when sooner or later a product batch proves to be impure. The processing of that impure batch is a substantial waste of time and materials. The present invention therefore provides a method in which, by means of sonic transmissions through the relevant part of the bed, it is determined from time to time whether such permanently-bound adventitious substances have reached a predetermined threshold position in the column corresponding to an operational limit at which the column needs to be emptied and repacked. This procedure promotes confidence and consistency which are of high importance with these technologies.

A final aspect disclosed herein relates again to packing rather than running the column. During the packing process, sonic transmissions according to any of the above proposals are used to identify a time at which the advancing bed front has nearly reached the top of the bed space. In dependence on that detection, the control system switches the pump control to act in dependence on

a detected packing pressure. When a dip in packing pressure characteristic of complete packing is observed, the pump is turned off. Correspondingly programmed apparatus is again an aspect protected herein. To explain: it is well known to those skilled in packing chromatography columns that a characteristic dip in packing pressure is seen just as the column becomes full. It is undesirable to continue to apply the pump beyond this stage; a better pack is obtained if it is promptly turned off. With an opaque column, the packing operator must keep a careful watch for this. A continuous pressure-sensitive control of the pump is not desirable, however, because pressure fluctuations of comparable sizes occur at other stages of the packing when the pump should certainly not be turned off. By using a sonic transmission sensor to note when the bed is nearly complete and only then initiating the monitoring for a pressure dip, the virtues of these respective techniques are happily combined.

Tests underlying the present proposals, and examples of apparatus and procedure, are now described with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig 1 is a schematic view of a chromatography column with an automated packing system;

Fig 2 shows ultrasound speed measurements across the

column during a trial pack;

Fig 3 shows similar measurements but with a greater degree of temperature control;

Figs 4,5,6 and 7 are data showing relations between pack parameters and pack quality for a Sepharose (gel) medium;

Figs 8,9 and 10 are packing data from 5 runs for determining a relation between packing rate and pack quality for ceramic media;

Fig 11 shows a UV trace at the product outlet of the column in a test run with a sample of albumin;

Fig 12 is an ultrasound speed trace during the same run, showing a speed change through the albumin-occupied region of the column;

Fig 13 is a schematic view of a column packing system exploiting feed-back from ultra sound sensors and having a display, and

Fig 14 is a further schematic view illustrating the detection of permanently-bound impurities and of sample bands passing through the column;

Figs 15 to 19 are schematic views of apparatus set-ups and procedures exploiting the ultrasound detection facility, and

Fig 20 shows a packing 'skid' embodying the invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

With reference to Fig 1, a chromatography column 1 is provided with upper and lower packing valves vc1, vc2 of the kind described in our WO-A-96/10451 to which reference should be made. The packing flow system includes a larger pump p1 for packing and for spraying the column top when unpacking, a smaller pump p2 also for packing and enabling suction from the bottom of the column when unpacking, tanks S, L to hold a slurry of packing medium and particle-free liquid respectively, a four-way valve v1 controlling the inlet to the pump p1, a four-way valve v2 controlling the outlet from the pump p1 as between the top and bottom of the column, a three-way valve v3 controlling the inlet to the pump p2 from the column or tank, a three-way valve v4 controlling the outlet from the pump p2 to the column or the tank, and a three-way v5 controlling a return from the column top to the tank or to a vent. For a description of a suitable enclosed (injected) packing procedure, refer to e.g. WO-A-96/10451, GB-A-2258451 or WO-A-99/64130 as mentioned previously.

In the present work the column was a variable-length 600mm diameter column, operated at a bed height of 160mm.

TEST 1: RECOGNISING THE FRONT

In a first set of tests Sepharose 4 medium was used, slurried in distilled water. By way of illustration, the

following Table 1 shows the variation of various parameters as the pack proceeded. Ultrasound transceivers 2,2a (Fig 1) were secured to the outside surface of the column wall about a third of the way up the bed. The speed of sound through the column interior as measured between these is given in Table 1. The tabled values are purely illustrative. Figs 2 and Figs 3 show plots of the sound speed between the ultrasonic transceivers 2,2a and time in two different runs. Fig 2 shows an initial phase I during which the sound speed increased gradually, followed by a discontinuity at which the advancing bed front rose past the transceivers - the column used was a transparent-walled-one for reference, so this was seen to happen - and a second phase II where the sound speed through the medium bed was appreciably higher. Sound speed is significantly dependent on temperature. Investigations showed that the gradual rise in phase I was due more to temperature changes than slurry density phenomena. Indeed, more scrupulous temperature control of all the materials resulted in the Fig 3 plot where the speed of sound through the unpacked region of the column remained essentially constant until the clear discontinuity when the bed front rose past the transceivers 2, 2a. These experiments confirmed the ease of identifying the bed front using ultrasound.

TEST 2: QUALITY OF PACK, AND ACCUMULATION RATE

A further set of tests was then carried out using a ceramic medium. The study and its results were as follows.

SUMMARY

Ceramic medium (BioSepra Q Hyper DF) was packed into a 400mm diameter column to a 200mm bed height. The buffer, packing pressure and slurry concentration were varied. The two best repeated results were obtained by 0.025M Tris HCl adjusted to Ph adjusted 7.5 with NaOH. The slurry concentration was 50% and the end packing pressure in the column was 1.5 bar. The flow rate at the start was initially 1000cm/hr.

In the light of our work, it appears that at the start of the pack the bed height build should be at say from 25-30mm/minute for the first third of the total packing time. After this stage the rate should increase to for example 75-80mm/minute until the column is filled. For a 200mm bed height, near the completion of the pack of the flow may be pulsed between 300 and 900cm/hr. The pack can be considered complete when the pump stalls, usually after 3-4 minutes for a 200mm bed height.

It appears from the work (described below) that there is a packing rate "corridor" in terms of rate of bed height accumulation which has an appreciable width and which if kept to can lead to a better pack. An actual packing rate/time path following such a corridor

can be regarded as a fingerprint of an optimised packing process. That is to say, if the packing operative keeps the packing parameters so that the rate of bed accumulation is within the upper and lower bounds of the prescribed "corridor" then a good pack can be predicted. This "fingerprint" or pack profile can then be used in production as a practical aid via automation and as a validation parameter for a column.

DESCRIPTION OF WORK

The column used was a variable bed height Mark II Euroflow column (EQ400-V-EQ911, with steel meshes). The medium has already been identified.

Before packing the medium was de-fined three times in slurries at about 30% concentration. The slightly cloudy supernatant was pumped away. The column was fully primed with buffer before all packs. Slurry was pumped in via the top nozzle (it can be done through the bottom) and the slurry liquid left via the mobile phase path at the bottom of the column. The packing pressure was measured at the top mobile phase port. The slurry was pumped by a Husky 715-diaphragm air-driven pump.

Bed quality evaluation was by injecting one litre of a 1% acetone solution in water under the column using up flow and down flow at a variety of flow rates, before and after an 18 hour test period for bed stability. The same was done with mobile phase in 0.025 M Tris HCl adjusted

to pH 7.5 with NaOH.

Table 2 details the 13-stage test conditions used. Table 3 displays the 100cm/hr flow rate (2l/minute) results based on the lowest HETP, being those obtained nearer the 100cm/hr results. Results are shown for before and after the stability test delay.

Fig 4 of the drawing shows the packing profile for each of the five packs indicating the quality (in terms of plates) of the pack achieved. The graph shows the rate of build-up of the bed during packing; this rate of build up is of course a complex result of flow and pressure conditions in the column during packing at the relevant stage.

The results indicate that the ceramic medium could be packed in the 400mm diameter column to a 200mm bed-height to a quality of over 4000 plates per metre with asymmetries of about 1.4. Two repeats gave similar results.

Fig 5 adds to Fig 4 by including linear regressive approximations to the respective curves, and their radiance. Fig 6 shows that there is a correlation between the gradient (i.e. the rate of bed build-up in mm/minutes) and the plate number (quality) of the resulting bed.

Of course these straight-line regressions are crude approximations. Table 4 below gives a better analysis by

dividing the packing procedure into 3 stages.

Observations from Table 4 are listed below.

1. The 'good' packs (Pack 2 and 3) share very similar rates at start middle and end. The first build up of the bed is the slowest part. Then the rate at which the bed builds increases at Phase 2 perhaps because the supernatant slurry concentration increases. This higher rate is held constant for Phase 3.
2. The 'satisfactory' packs (Packs 1 and 4) deviate from the successful profiles significantly at the later part of the pack. Their initial build up rates are quicker than the 'good' packs. Their 2nd and 3rd Phases are very different yet they yield similar results.
3. The 'poor' pack (Pack 5) profile deviates the most from the others. The initial build up is low or similar but the 2nd phase is 4 to 8 times slower. Phase 3 increases but is still half that of the Phase 3 rates of the good packs.

Some conclusions based on these observations are listed below:-

1. During the first phase where media initially builds up on the bed support the rate needs to be slower than the later Phases. Perhaps to avoid blinding

the mesh with high velocity media that has little or no back pressure.

2. If the 2nd Phase is equal or slower than the 1st Phase the result is very poor (Pack 5). Perhaps the slower rate allows the layer against the bed support to mix and lose its packing density or homogeneity. Thus a quicker 2nd Phase rate is needed to hold down the 1st layer.
3. The 2nd Phase can be very different to the 3rd Phase and still yield satisfactory packs (Packs 1 and 4) - it is not catastrophic.
4. To achieve better packs the 2nd and 3rd Phases are preferably about three times faster than the 1st Phase. They may be at about the same rate. This may helps homogeneity throughout the rest of the bed.

Based on these results it appears that there is a packing rate 'corridor' of varying width that can be followed to achieve a 'good pack'.

Figs 11,12 show the result of an experiment in which a column set-up as shown in Fig 1 had applied to it a sample pulse of 10% albumin. Fig 12 indicates that the albumin passed as a band or pulse through the column as detected by UV detector at the column exit. Fig 11 shows the interesting results from the ultrasound sensor,

namely that the passage of the band past the sensor correlated with a band of increased ultrasound transmission speed through the column. This is marked B.

Figs 13,14 show schematically an apparatus set up embodying the invention, with a linear array 20 of numerous piezoelectric transceivers applied up one side of the column, with a corresponding array 21 on the opposite side. They need not be exactly opposite; in particular a slight offset helps to avoid difficulties adjacent the ends of the column if there is a projecting central packing nozzle. The drawings show schematically the front 5 of a bed 16 rising up the column as packing proceeds. A programmed control unit 4 - a conventional microprocessor - is fed with the inputs from the sensors and programmed with desired target data for the target rate profile. The packing pump P is controlled accordingly. An external display 3 is provided which may show the sound impedance or speed in bar form against the height up the column. Fig 14 shows a similar apparatus being used at a different stage, when the column has been packed and is in use. One aspect of the use is shown at the top of the bed. A band of accumulating permanently-bound contamination is gradually extending down into the bed from the top. This affects the ultrasound transmission from the top sensors and is therefore shown on the display at 'A'. When it reaches a critical level

CL the program issues a warning to the user that the column is effectively spent.

A band of material 6 is also shown, progressing down the column. This is material being purified. Despite the opaque column wall, its progress can be followed (peak B) on the visual readout of the ultrasound data.

Figs 15 to 19 show schematically these and other functionalities of the proposed column arrangement having the array of ultrasound sensors extending axially.

Fig 15: column 1, sensor array 20, control processor 4, data logger 31, pump P. Basic 'fingerprinting' of a pack profile, plus pump control, using feedback.

Fig 16: packing, with tracking of the accumulating bed on display 3.

Fig 17: packing method using additional control parameter of packing pressure at meter 25. Detect when column nearly full, open time window of sensitivity to pressure drop, pressure drop signals pack complete, pump stopped and valves moved to 'run' positions for chromatography.

Fig 18: display 3 indicating void or inhomogeneity 62 in the column contents.

Fig 19: tracking a band 6 of valuable component through the column display 3 or band 'B'.

Fig 20: shows a packing station or 'skid' i.e. a movable trolley having a packing pump P and the

associated valve connectors V, operatively controlled by processor 4 adapted to receive inputs from ultrasound detectors, initiate operation of transmitters, receive packing profile data and programmed to control the pump P accordingly.

Table 1

SLURRY	18°C	COLUMN PRIMING LIQUID	19°C		AMBIENT	19°C
PACKING PROFILE						
Packing Air Pressure Baseline, bar		Slurry through valve only litres/min		Slurry through valve only bar		
PACKING TIME	FLOW	PRESSURE	BED HEIGHT	MOTIVE AIR PRESSURE	SLURRY INLET PRESSURE	Speed of Sound
minutes	l/min	bar	mm	bar	bar	
0	36	0.25	0	3		1478.6
1	36	0.15	15	3		1479.3
2	27	0.2	45	2.5		1479.9
3	25	0.4	85	2.5		1480.2
4	17.2	0.55	105	2.5		1480.3
5	14.8	0.65	130	2.5		1479.8
6	14	0.65	155	2.5		1490.6
7	14	0.65	160	2.5		1490.8

Table 2

SHOWING THE TEST CONDITIONS USED		
Volumetric flow rate l/min	Linear flow rate cm/hr	Flow direction
3	150	Down
2	100	Down
1	50	Down
1	50	Up
2	100	Up
3	150	Up
318 hour stability run	150	Down
3	150	Down
2	100	Down
1	50	Down
1	50	Up
2	100	Up
3	150	Up

Table 3

Pack Number	Results	Before Stability: Downflow	Before Stability: Upflow	After Stability: Downflow	After Stability: Upflow	Mean	Packing Differences to B2 and B3
B1	Pl/m	3384	n/a	3100	n/a	3242	Packed in PO_4 buffer at 1.3 bar
	Asymmetry	1.5	n/a	1.25	n/a	1.375	
B2	Pl/m	4881	3842	3857	3770	4088	-
	Asymmetry	1.4	1.4	1.4	1.3	1.4	
B3	Pl/m	4308	4328	4267	4147	4263	-
	Asymmetry	1.4	1.4	1.5	1.6	1.5	
B4	Pl/m	3485	3449	3142	3112	3297	5 minutes to pack 1.4 bar. Before stability downflow at 50 cm/hr
	Asymmetry	1.4	1.4	1.6	1.8	1.6	
B5	Pl/m	2443	2161	2597	2398	2400	Took 7 minutes (stopped & started) to pack at 2.2 bar
	Asymmetry	1.1	1.8	1.5	1.4	1.5	

Table 4: Comparing the Pack Profiles as Observations from Graph

Pack Number	Plates/metre (2 sig. Fig.)	Initial Third of Pack Phase 1	Middle Third of Pack Phase 2	Final Third of Pack Phase 3
		Packing Rate mm/min		
1	3200	33	40	60
2	4100	26	82	65
3	4200	27	77	77
4	3300	41	50	26
5	2400	24	11	39

CLAIMS

1. Chromatography process in which a particulate medium is packed into a bed space of a column housing to form a close-packed bed filling the bed space and a process liquid containing components to be separated is passed through the packed bed to separate the components, characterised by transmitting an ultrasound signal through the bed space and detecting the transmitted signal to determine a state or position of said particulate medium in the bed space.

2. Chromatography process according to claim 1 comprising monitoring the speed of transmission of the ultrasound signal through the bed space.

3. Chromatography process according to claim 1 or 2 comprising monitoring the attenuation of the transmitted signal.

4. Chromatography process according to any one of the preceding claims comprising said ultrasound signal transmission through the bed space during packing of the particulate medium into the bed space via a port in the wall of the column housing, as a pumped slurry.

5. Chromatography process according to claim 4 in which one or both of packing pump pressure and particulate medium slurry concentration is/are controlled in dependence on the packing status determined from the ultrasound signal detection.

6. Chromatography process according to claim 4 or 5 in which detected ultrasound signals are transmitted transversely to the direction of accumulation of the packed bed of medium.

7. Chromatography process according to any one of claims 4 to 6 in which detected ultrasound signals are transmitted through the bed space at plural locations distributed along the direction of accumulation of the packed bed of medium.

8. Chromatography process according to claim 7 in which a real-time rate of advance of the front of the accumulating bed, determined from its detected passage past plural locations as mentioned, is compared with a predetermined target rate of advance value and the packing pump pressure and/or slurry concentration adjusted as necessary.

9. Chromatography process according to claim 7 or 8 in which respective real-time rates of advance are determined for a plurality of said locations and compared with respective target values constituting a predetermined packing profile, and feedback control signals sent to a packing pump in dependence on the comparisons.

10. Chromatography process according to claim 9 in which said predetermined packing profile prescribes an initial phase with a slower rate of advance than in a subsequent main phase.

11. Chromatography process according to any one of claims 4 to 10 in which a control processor, operatively connected to the packing pump and ultrasound detection arrangement, is loaded with target packing data from a discrete data carrier, and controls the packing pump in dependence on comparisons between the detected and target data.

12. Chromatography process according to any one of claims 4 to 11 in which a detected ultrasound transmission adjacent that end of the bed space last filled by the accumulating bed is used to detect the arrival of the advancing bed front and thereby initiate reduction or cessation of pump operation at the end of the packing procedure.

13. Chromatography process according to any one of claims 4 to 12 in which a control processor is programmed to respond to a detected dip in packing pressure, corresponding to the bed space becoming full of medium, by turning off the packing pump.

14. Chromatography process according to any one of the preceding claims comprising said ultrasound transmission through the bed space during the passage of process liquid through the packed bed, to detect the presence and/or position of a said component in or passing through the bed.

15. Chromatography process according to claim 14 in which detected ultrasound transmissions at plural locations along the packed bed are used to track the

progress of a band of a said component passing through the bed.

16. Chromatography process according to any one of the preceding claims in which a detected ultrasound transmission through the packed bed adjacent an input end for the process liquid is used to determine the extent of encroachment of bound impurity into the bed from the input end.

17. Chromatography process according to any one of the preceding claims, carried out using apparatus according to any one of the following claims.

18. Chromatography apparatus comprising a chromatography column having a housing wall with side wall and end wall portions defining an internal bed space for containing a particulate packing medium, characterised by at least one ultrasound transmitter on the housing wall, disposed to transmit an ultrasound signal through the bed space, and a detector to detect the transmitted signal.

19. Chromatography apparatus according to claim 18 in which at least one said ultrasound transmitter is comprised in a transceiver unit also comprising a said detector.

20. Chromatography apparatus according to claim 18 or 19 in which said transmitter and/or detector is on the outside of the housing wall, so that the ultrasound signal is transmitted to the detector through the wall as well as through the bed space.

21. Chromatography apparatus according to any one of claims 18 to 20 in which plural said transmitters and/or plural said detectors therefor are distributed along the column in a direction between an inlet and an outlet of the column.

22. Chromatography apparatus according to any one of claims 18 to 21 in which the column is a vertical cylinder, e.g. with a steel side wall.

23. Chromatography apparatus according to any one of claims 18 to 22 comprising a control processor operatively connected to the ultrasound transmitter and detector and programmed to determine a speed and/or attenuation for the transmissions between them via the internal bed space.

24. Chromatography apparatus according to any one of claims 18 to 23 in which the chromatography column has a port through its housing wall adapted for the injection of a slurry of particulate medium for packing the column.

25. Chromatography apparatus according to claim 24 in which plural said transmitters and/or plural said detectors are distributed along the column to enable detection of ultrasound transmissions along a corresponding plurality of paths through the internal bed space.

26. Chromatography apparatus according to claim 25 in which a control processor is operatively connected to the transmitters and detectors and programmed to determine,

for said plurality of transmission paths, respective transmission speeds and/or attenuations.

27. Chromatography apparatus according to claim 26 in which the control processor is programmed to detect successive positions of the front of an accumulating packed medium bed in the column by means of the change in transmission characteristics as the front crosses respective transmission paths, and to

determine a real-time rate of advance for said front;

compare the real-time rate of advance with a target rate of advance predetermined for the corresponding position on the column or stage of the process, and

generate a control signal to control a packing pump in dependence on the comparison.

28. Chromatography apparatus according to claim 27 in which the control processor has a data reader for reading a set of target data for the packing procedure, appropriate to the column and medium being packed, from a discrete data carrier.

29. Chromatography packing apparatus for use in packing a particulate medium into a chromatography column having a column wall having a housing wall with side wall and end wall portions defining an internal bed space, with a packing port through the housing wall for introduction of a slurry of the particulate medium in a carrier liquid;

the apparatus comprising a motorised pump for pumping the slurry to the packing port and a control processor connected to control the output of the pump, the control processor having one or more inputs to

receive the detected signals from one or more detectors for ultrasound transmissions and being programmed to adjust the output of the pump in dependence on detected signals.

30. Chromatography packing apparatus according to claim 29 in which the control processor is programmed to determine an advance rate based on the time elapsing between signals from two different ultrasound transmitter/detector combinations indicating a change to greater attenuation or greater speed of the respective transmissions, to compare the advance rate with a predetermined target value and to send a signal to increase, maintain or decrease the pump output according to whether the predetermined rate is less than, corresponds to or is greater than the predetermined target value.

31. Chromatography packing apparatus according to claim 29 or 30 comprising a set of the ultrasonic transmitters and detectors.

32. Chromatography packing apparatus according to any one of claims 29 to 31 comprising a data reader for reading a set of prescribed packing parameters for a given column and medium from a discrete data carrier.

FIG. 1

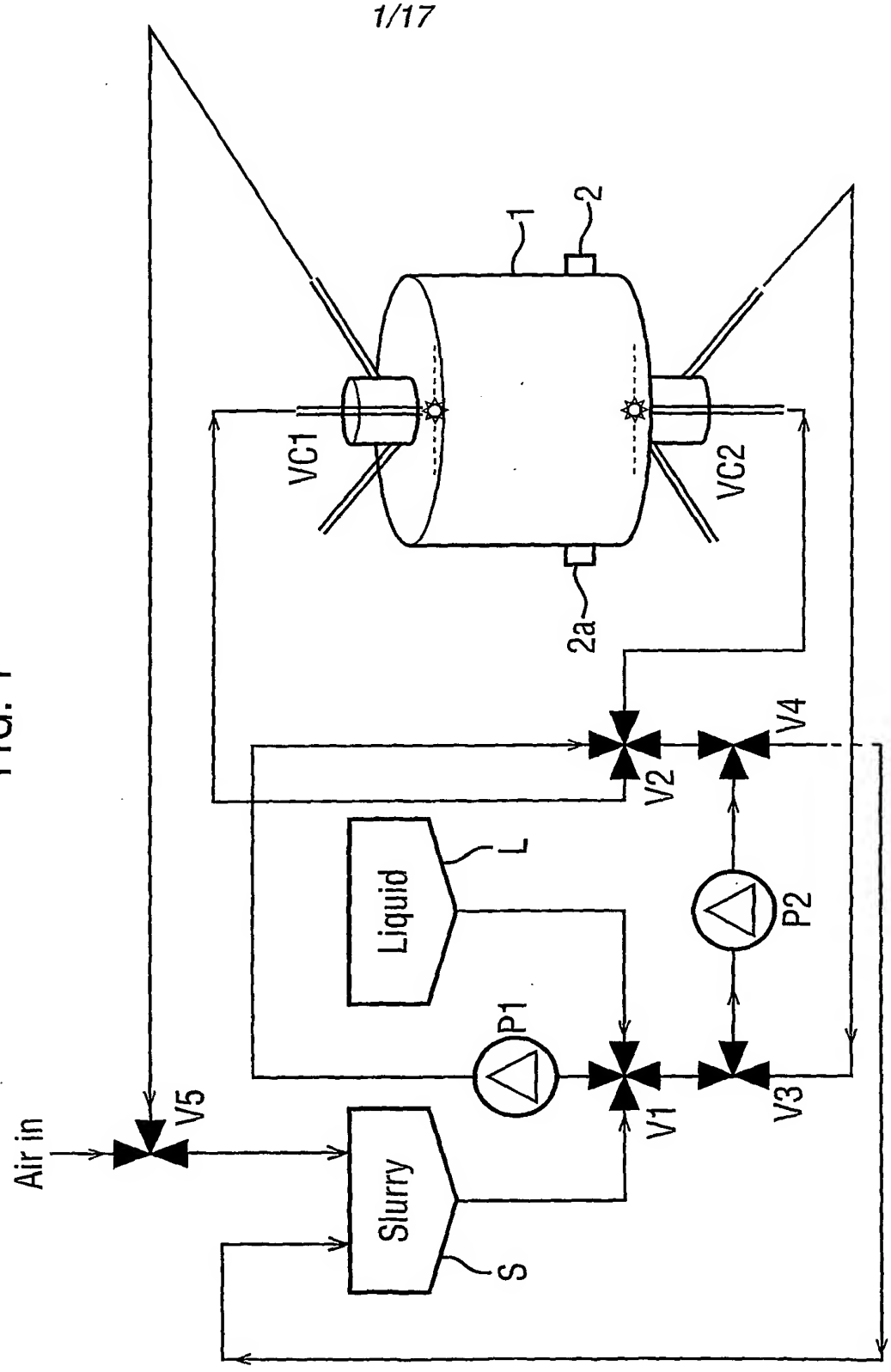


FIG. 2

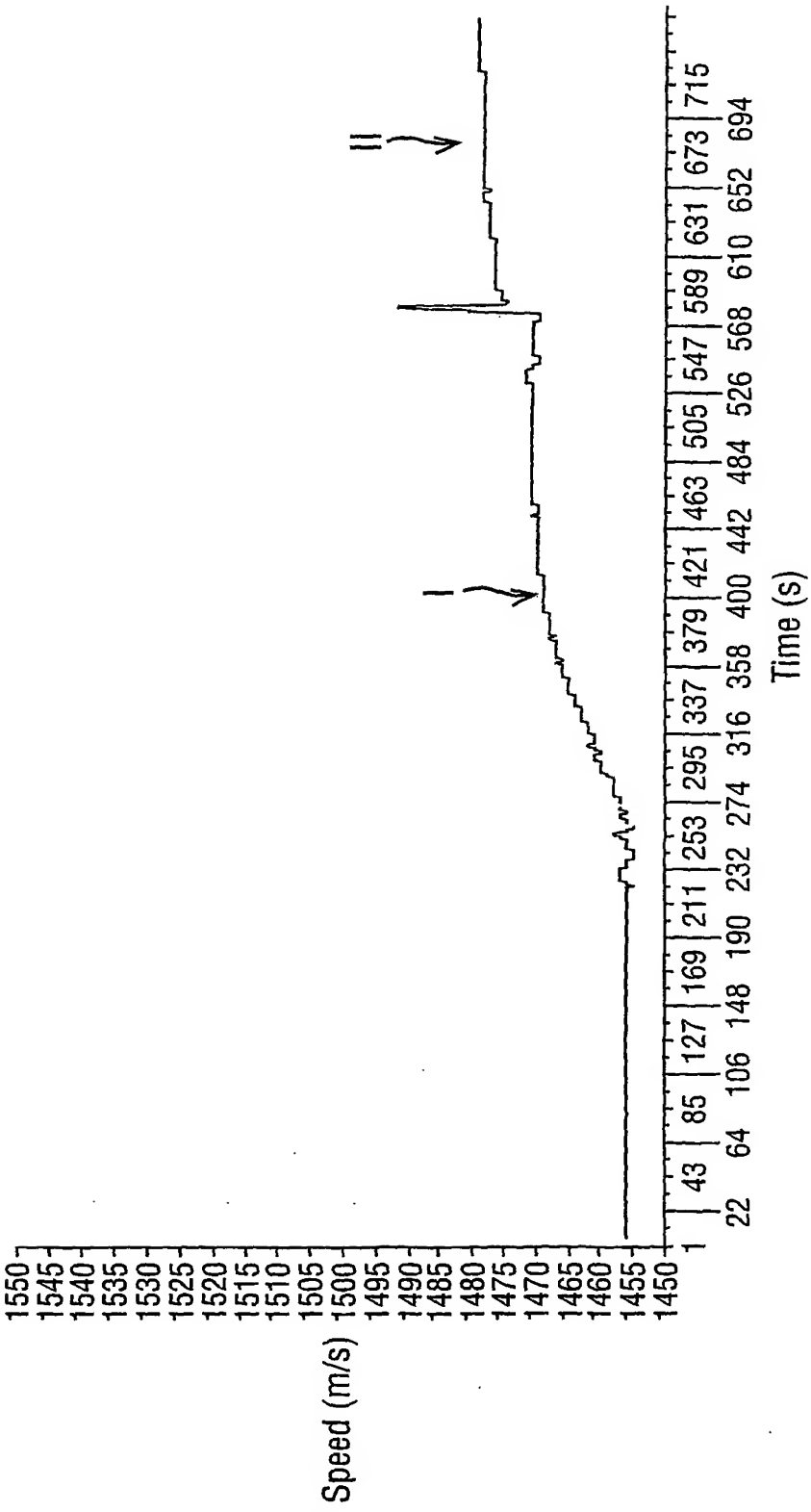

Speed (m/s)
1550
1545
1540
1535
1530
1525
1520
1515
1510
1505
1500
1495
1490
1485
1480
1475
1470
1465
1460
1455
1450
I
II
1 22 43 64 85 106 127 148 169 190 211 232 253 274 295 316 337 358 379 400 421 442 463 484 505 526 547 568 589 610 631 652 673 694 715
Time (s)

FIG. 3

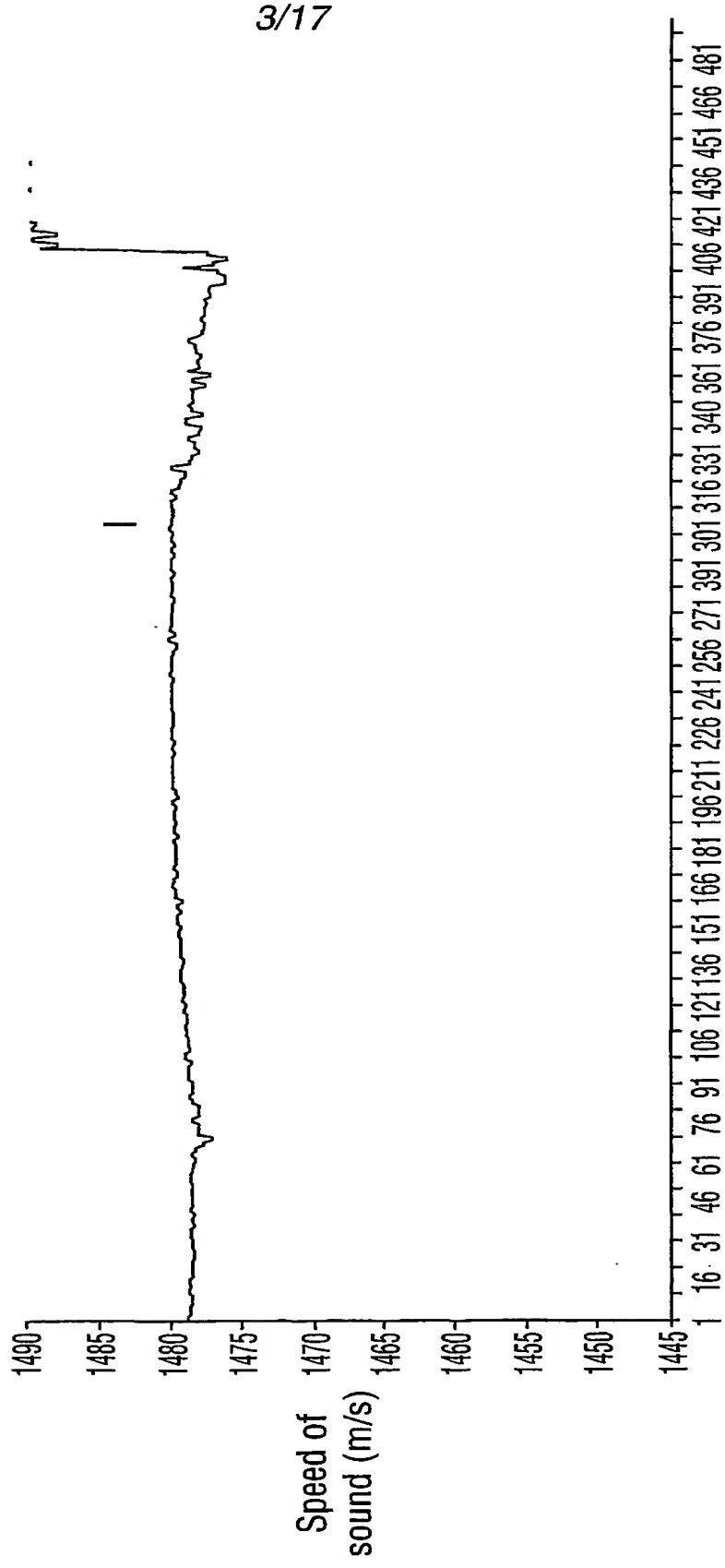

I
II
Speed of sound (m/s)
1490
1485
1480
1475
1470
1465
1460
1455
1450
1445
1 16 31 46 61 76 91 106 121 136 151 166 181 196 211 226 241 256 271 391 301 316 331 340 361 376 391 406 421 436 451 466 481
Time (seconds)

FIG. 4

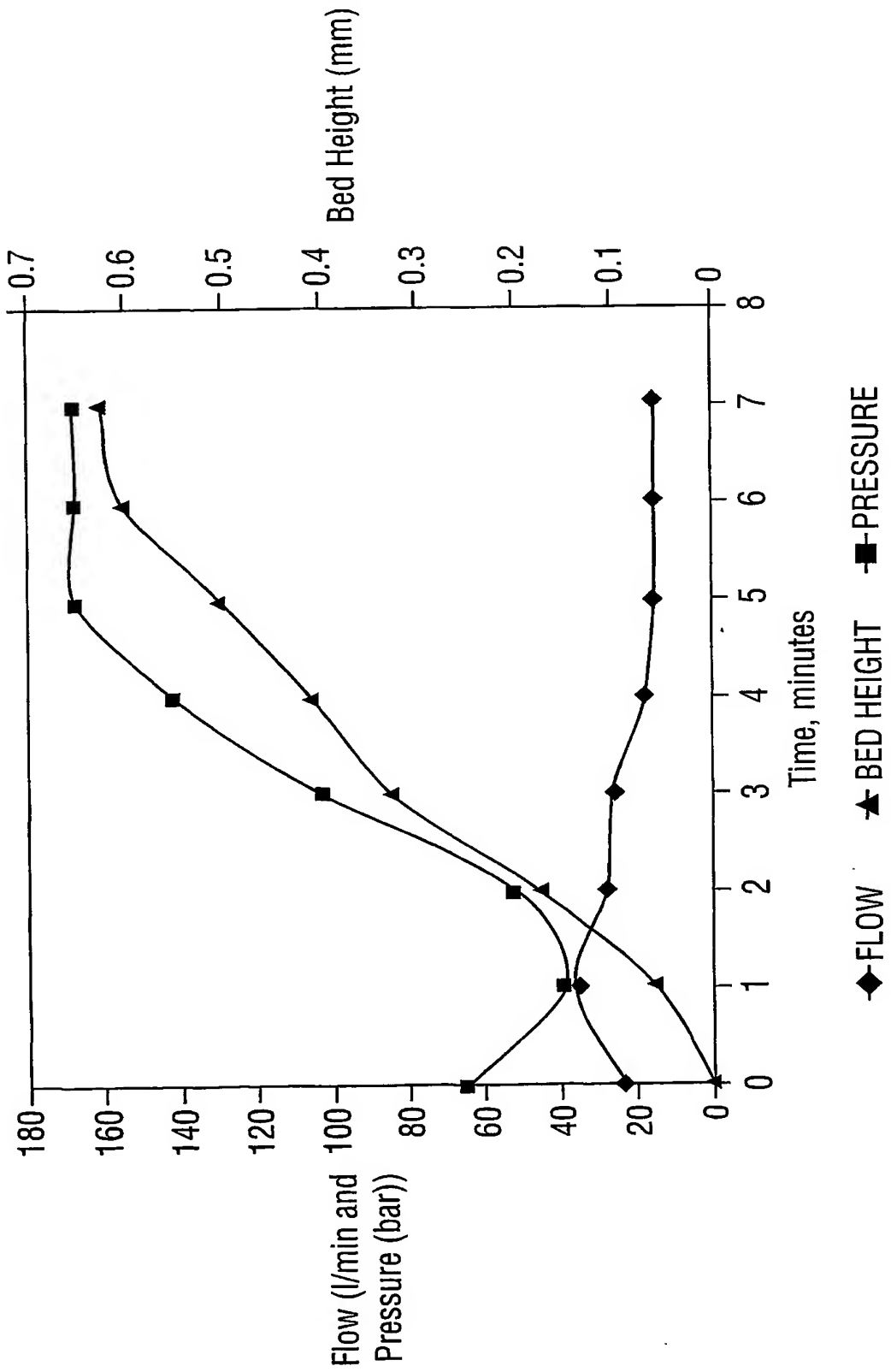

Bed Height (mm)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
180
160
140
120
100
80
60
40
20
0
Flow (l/min and Pressure (bar))
0
1
2
3
4
5
6
7
8
Time, minutes
FLOW
BED HEIGHT
PRESSURE

FIG. 5

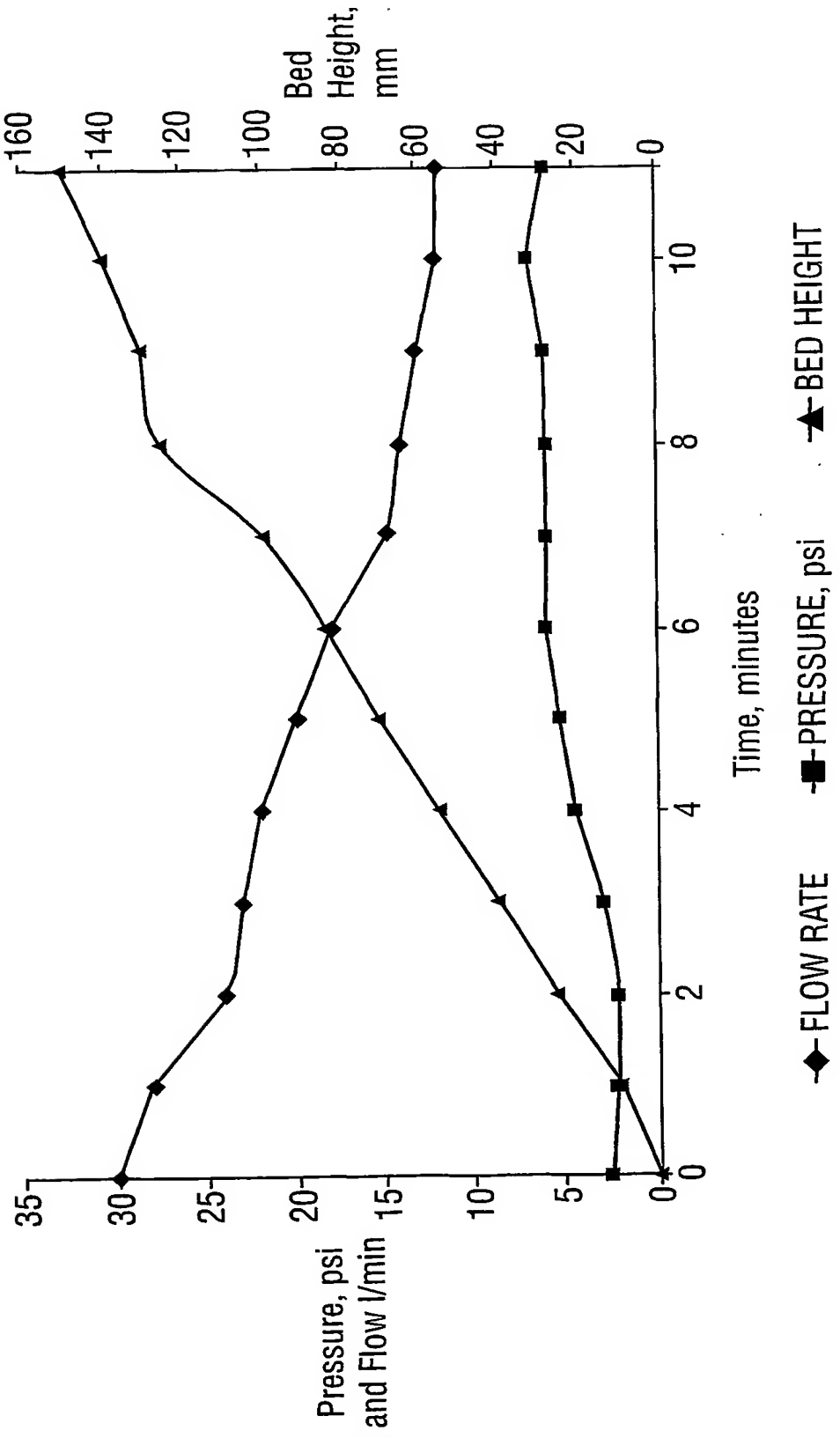

Bed Height, mm
160
140
120
100
80
60
40
20
0
Pressure, psi and Flow l/min
35
30
25
20
15
10
5
0
0
2
4
6
8
10
Time, minutes
FLOW RATE
PRESSURE, psi
BED HEIGHT

FIG. 6

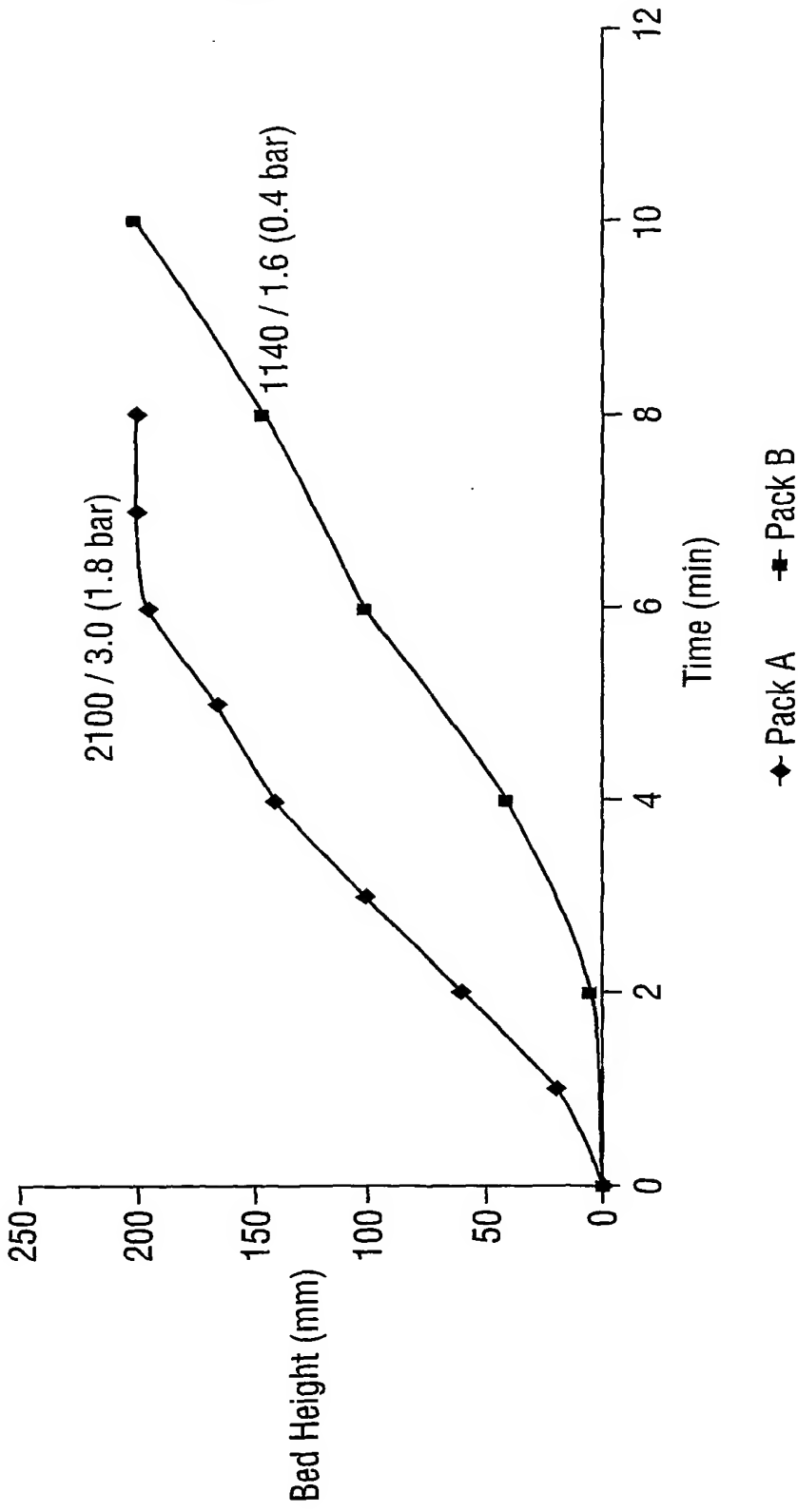

Bed Height (mm)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (min)
2100 / 3.0 (1.8 bar)
1140 / 1.6 (0.4 bar)
Pack A
Pack B

FIG. 7

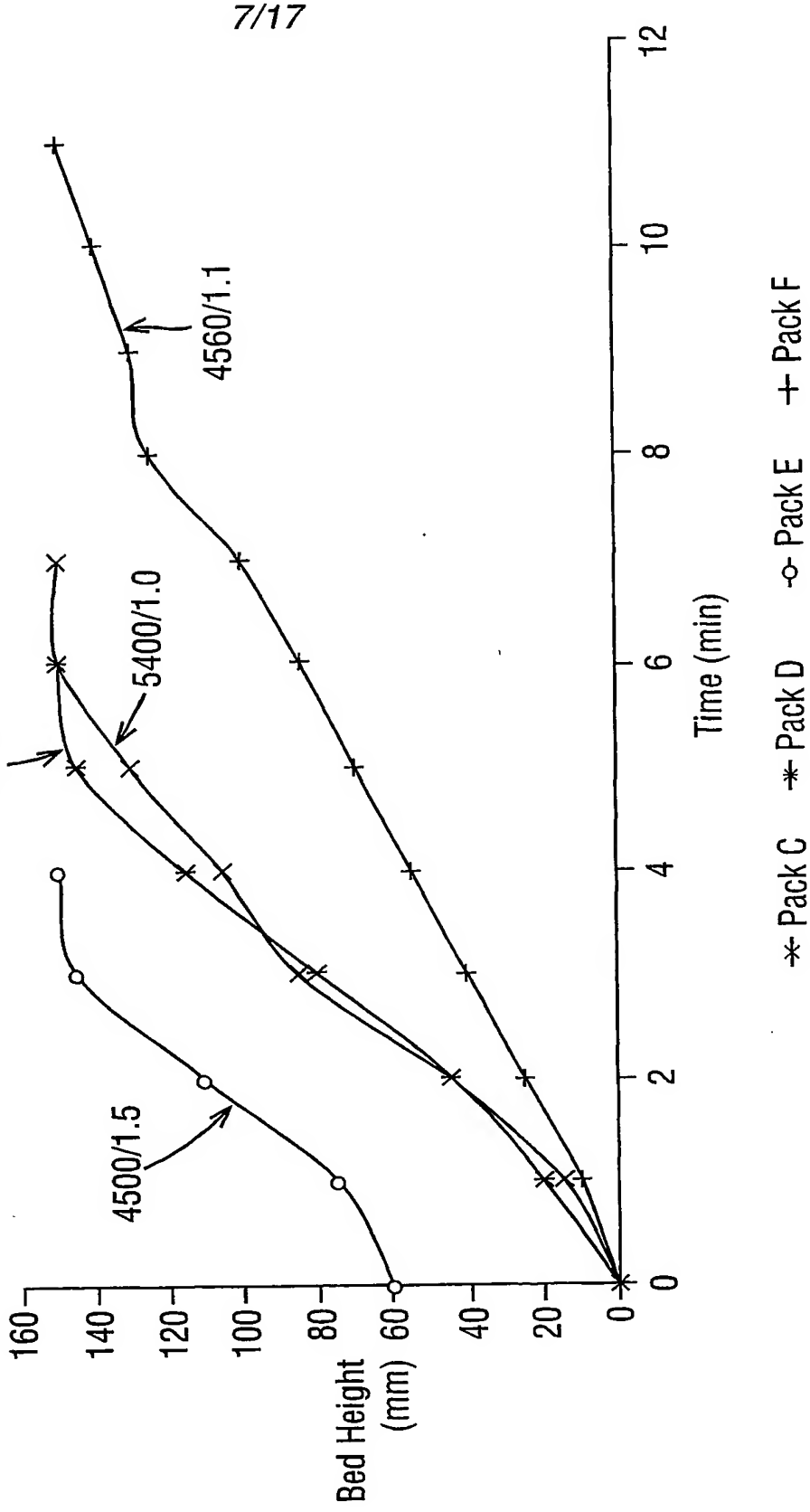

4440/1.1
5400/1.0
4560/1.1
4500/1.5
Bed Height (mm)
160
140
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (min)
Pack C
Pack D
Pack E
Pack F

FIG. 8

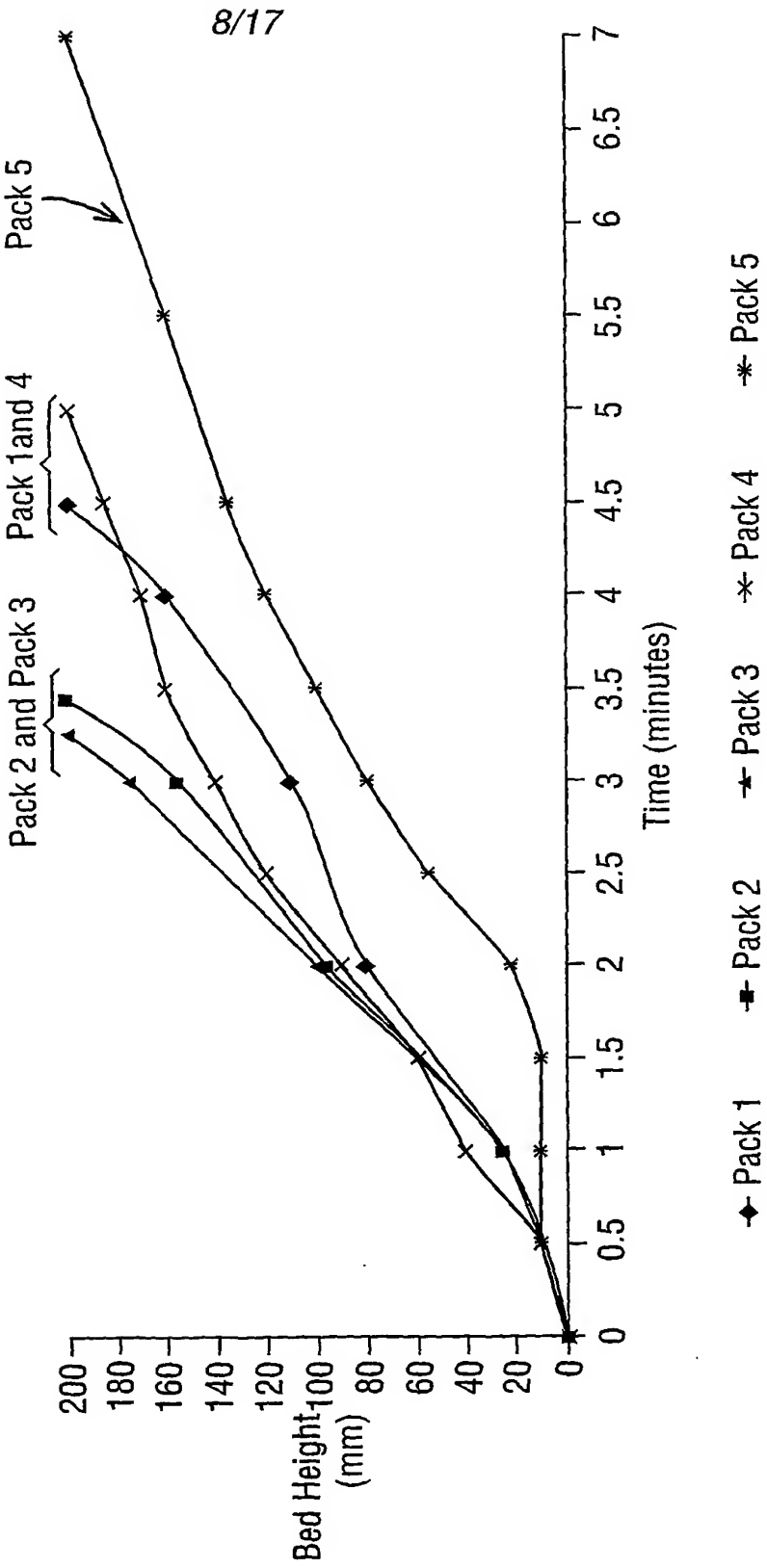

Pack 5
Pack 1and 4
Pack 2 and Pack 3
Bed Height (mm)
200
180
160
140
120
100
80
60
40
20
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
Time (minutes)
Pack 1
Pack 2
Pack 3
Pack 4
Pack 5

FIG. 9

Bed Height (mm)
0
20
40
60
80
100
120
140
160
180
200
Time (Minutes)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
Pack 1
Pack 2
Pack 3
Pack 4
Pack 5
Pack 1 Eq. y = 40.896x
Pack 2 Eq. y = 52.968x
Pack 3 Eq. y = 56.997x
Pack 4 Eq. y = 42.675x
Pack 5 Eq. y = 27.701x

FIG. 10

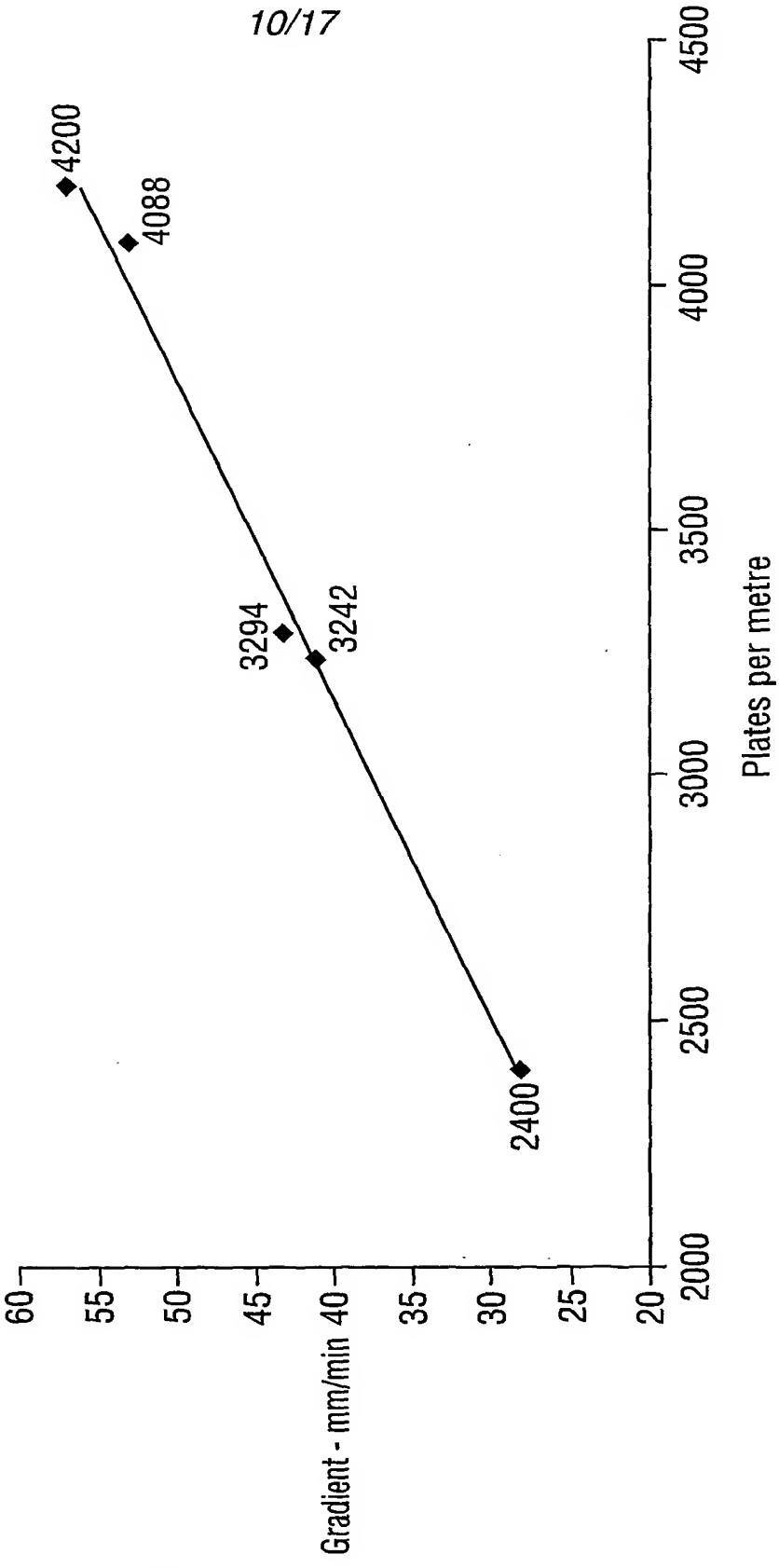

4200
4088
3294
3242
2400
60
55
50
45
40
35
30
25
20
2000
2500
3000
3500
4000
4500
Gradient - mm/min
Plates per metre

FIG. 11

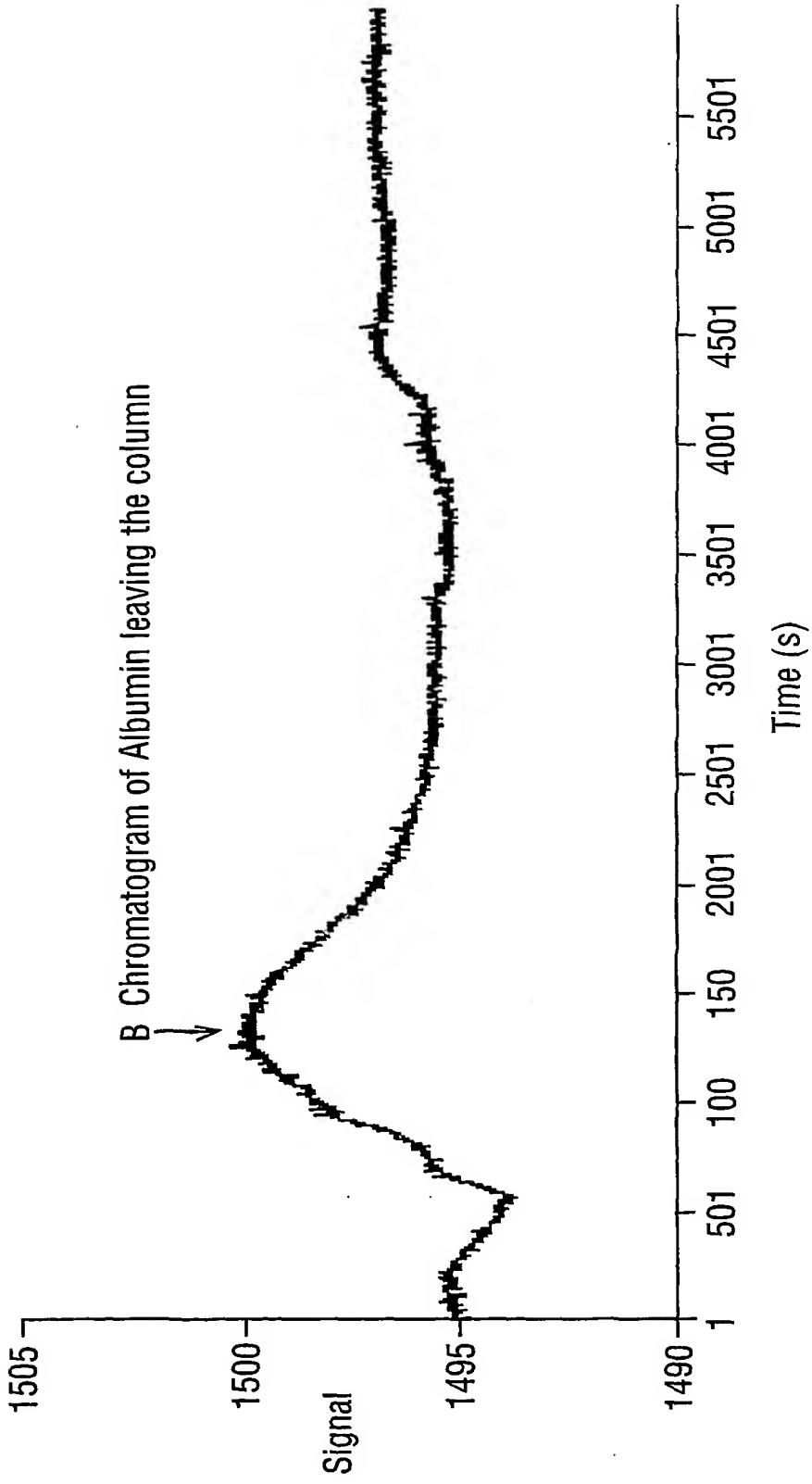

B Chromatogram of Albumin leaving the column
1505
1500
1495
1490
Signal
1
501
100
150
2001
2501
3001
3501
4001
4501
5001
5501
Time (s)

FIG. 12

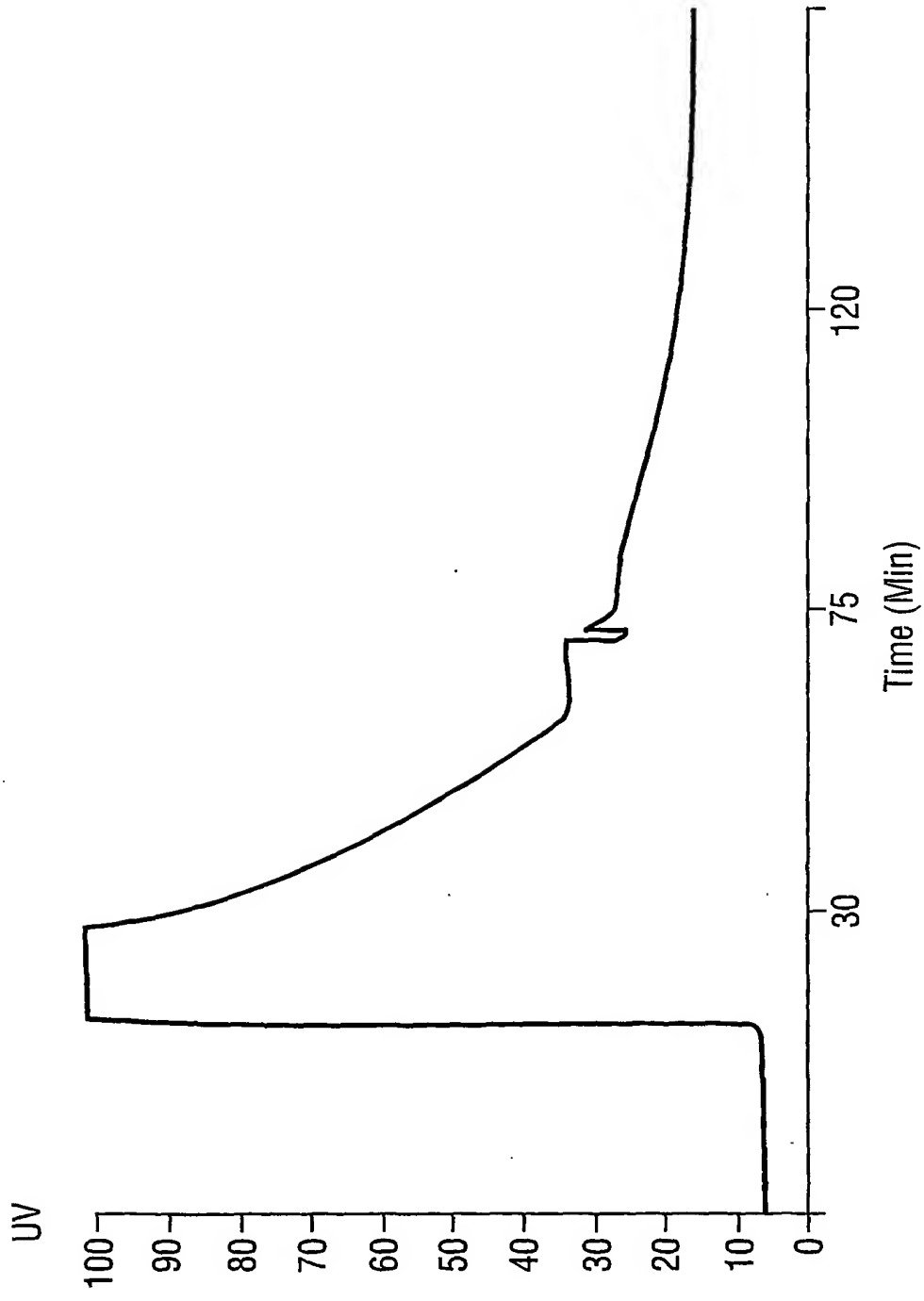


FIG. 13

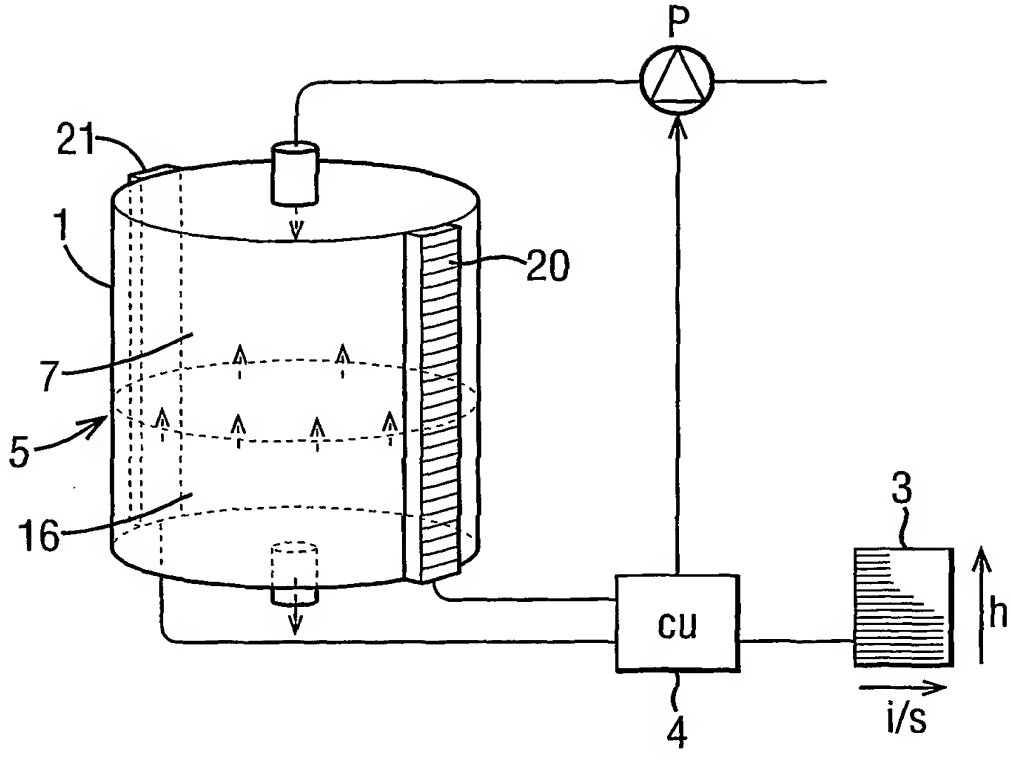
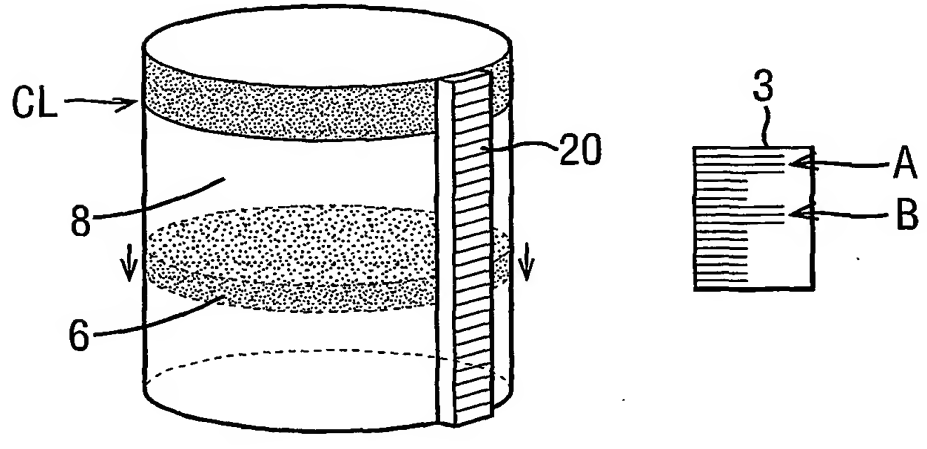


FIG. 14



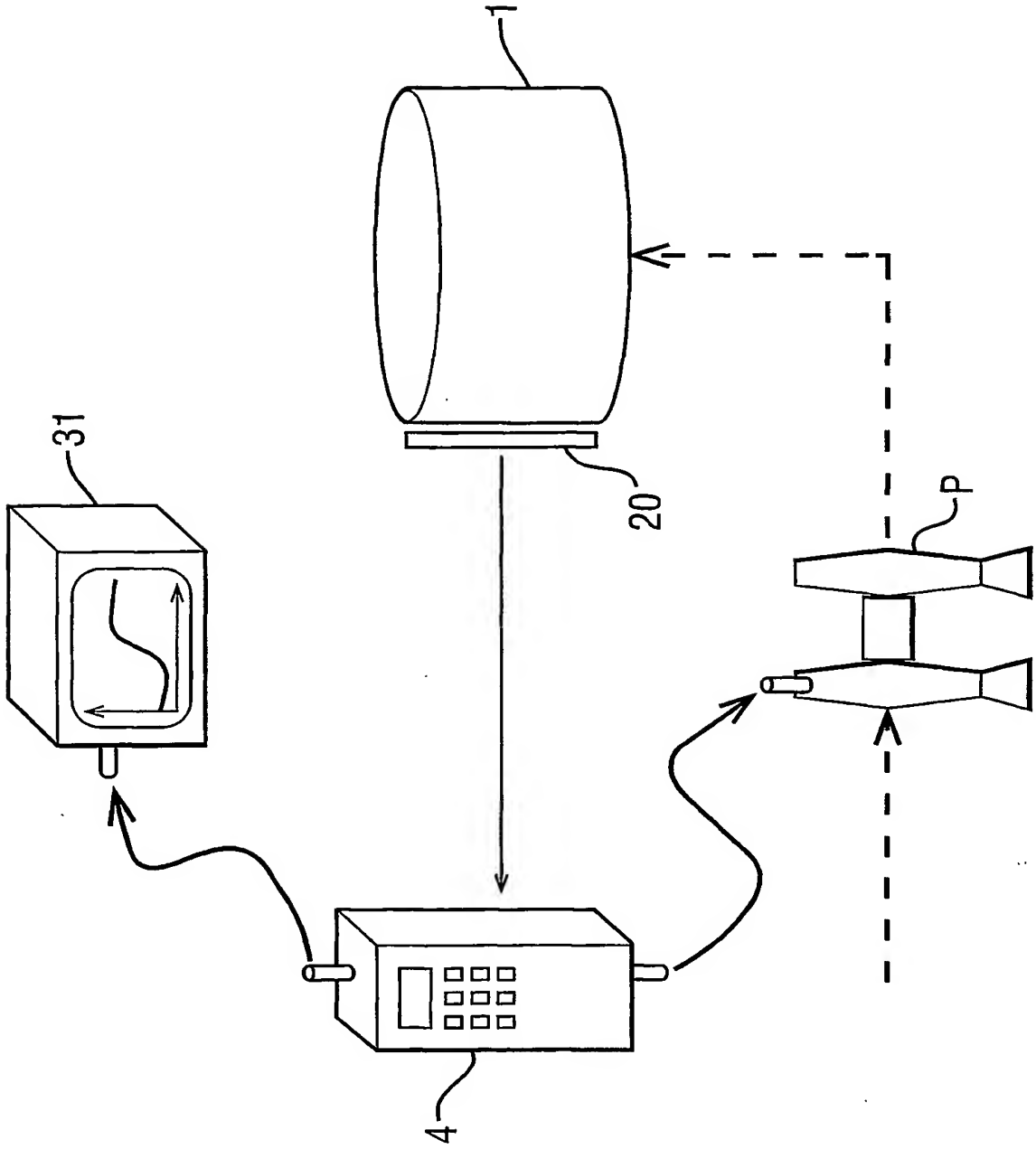


FIG. 15

FIG. 16

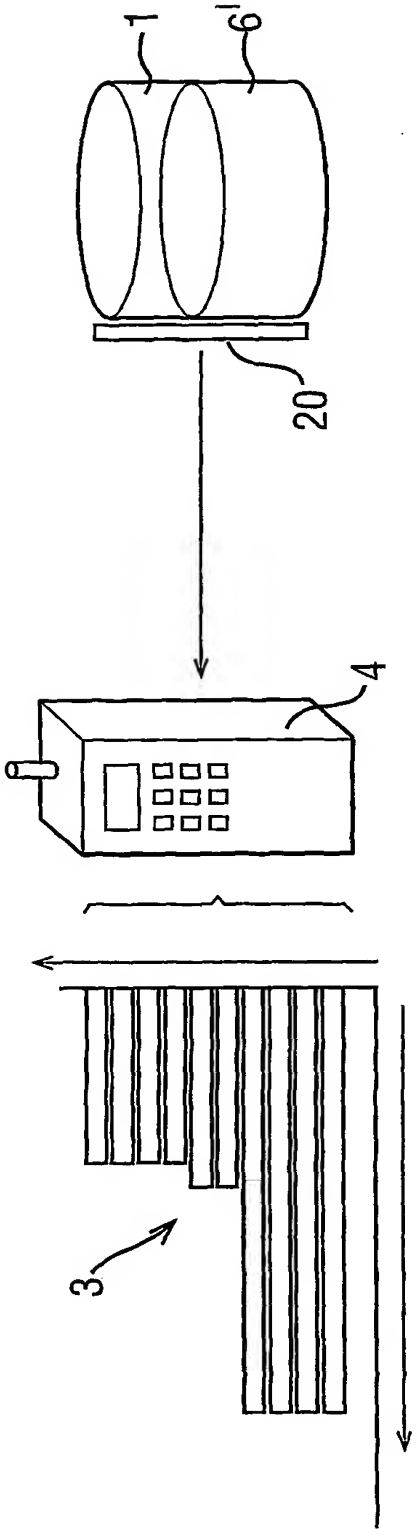


FIG. 17

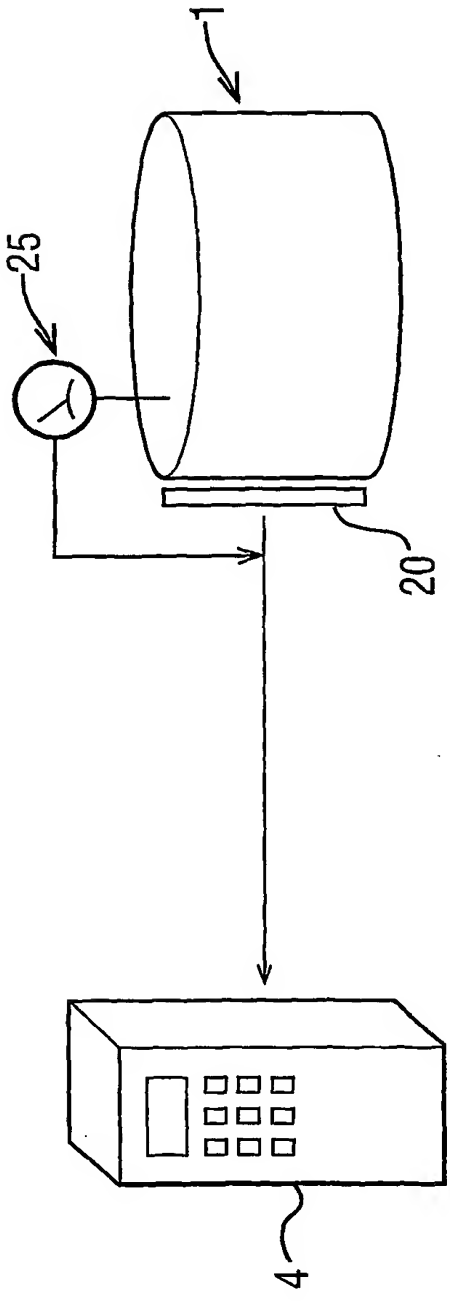


FIG. 18

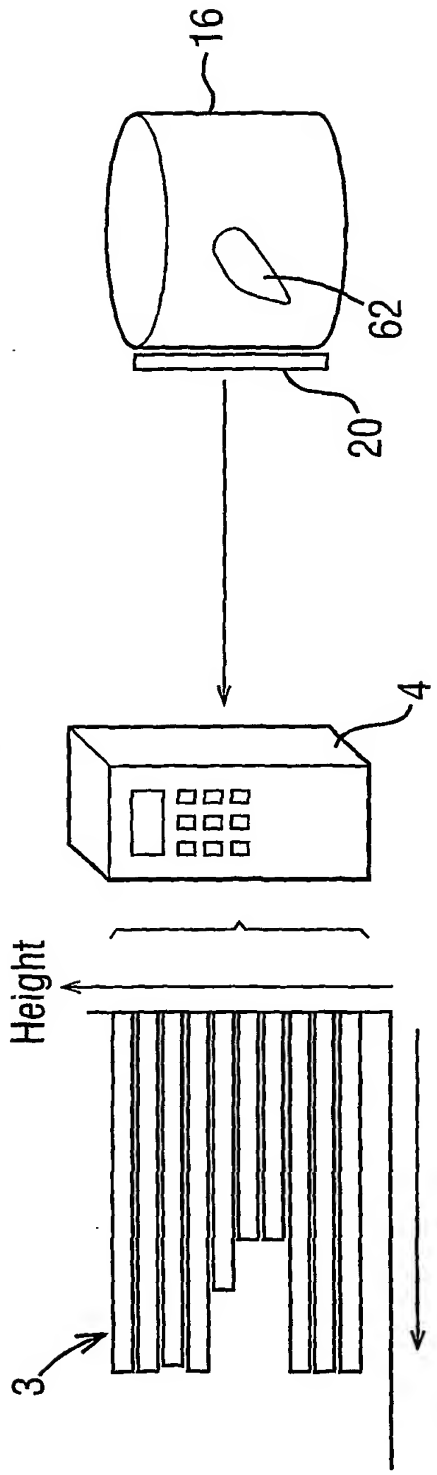


FIG. 19

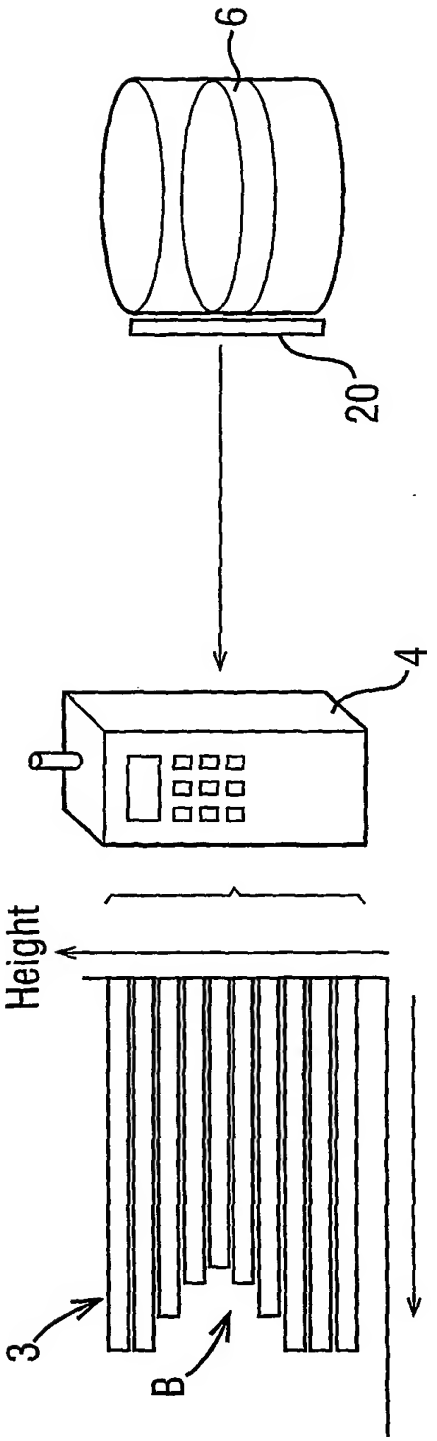
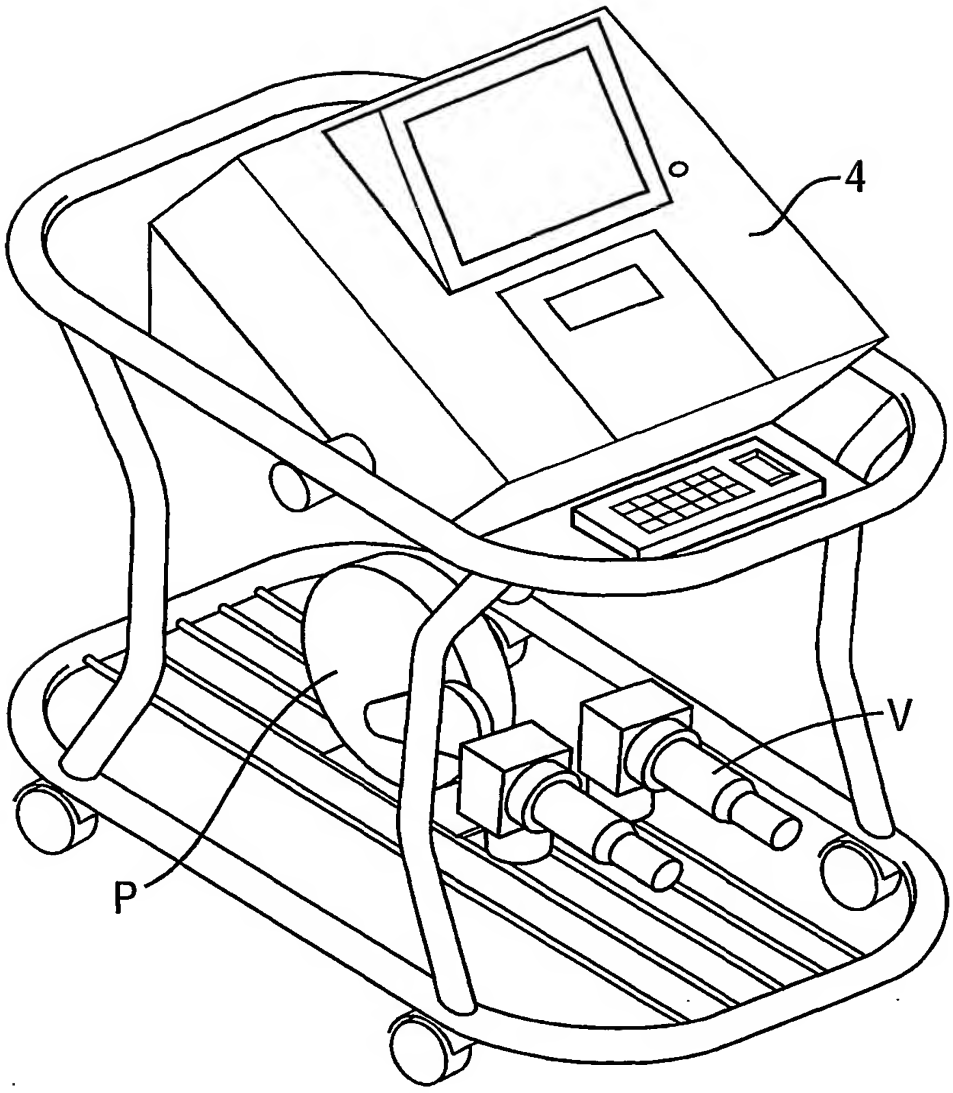


FIG. 20



INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/03403

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N30/56 G01N30/60 B01D15/08 G01F23/296

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N B01D G01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, COMPENDEX, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 061 371 A (TABATA TAKESHI ET AL) 29 October 1991 (1991-10-29) the whole document	1,4,5, 7-9, 11-15, 17-19, 21-32
X Y	GB 1 312 096 A (ECODYNE CORP) 4 April 1973 (1973-04-04) page 2, line 27-47; figure 1	1,2,4-6, 17,18, 22,24,29 2,3,27, 28,30
A Y	US 4 324 131 A (ROSENCWAIG ALLAN) 13 April 1982 (1982-04-13) column 2, line 20-47	1-32 2,3,27, 28,30

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2001	21/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Müller, T

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/03403

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5061371	A	29-10-1991	NONE		
GB 1312096	A	04-04-1973	BE	759217 A1	30-04-1971
			CA	941984 A1	12-02-1974
			CH	522209 A	15-06-1972
			DE	2057238 A1	24-06-1971
			ES	384863 A1	16-03-1973
			FR	2069813 A5	03-09-1971
			JP	48015143 B	12-05-1973
US 4324131	A	13-04-1982	NONE		

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
GPSBP5944723		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 01/03403	30/07/2001	28/07/2000
Applicant		
EUROFLOW (UK) LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   METHODS AND APPARATUS FOR PACKING CHROMATOGRAPHY COLUMNS AND CHROMATOGRAPHY COLUMN

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 13

   [X] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted] 01/03403

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N30/56 G01N30/60 B01D15/08 G01F23/296

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N B01D G01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, COMPENDEX, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X Y	GB 1 312 096 A (ECODYNE CORP) 4 April 1973 (1973-04-04) page 2, line 27-47; figure 1	1,2,4-6, 17,18, 22,24,29 2,3,27, 28,30
A Y	US 4 324 131 A (ROSENCWAIG ALLAN) 13 April 1982 (1982-04-13) column 2, line 20-47	1-32 2,3,27, 28,30

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but *cited to understand the principle or theory underlying the* invention

"X" *document of particular relevance; the claimed invention* cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled *in the art.*

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2001	21/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Müller, T

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[redacted] 01/03403

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5061371	A	29-10-1991	NONE		
GB 1312096	A	04-04-1973	BE	759217 A1	30-04-1971
			CA	941984 A1	12-02-1974
			CH	522209 A	15-06-1972
			DE	2057238 A1	24-06-1971
			ES	384863 A1	16-03-1973
			FR	2069813 A5	03-09-1971
			JP	48015143 B	12-05-1973
US 4324131	A	13-04-1982	NONE		

'CT REQUEST

GPSBP5944723

Original (for SUBMISSION) - printed on 30.07.2001 03:49:07 PM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.03.2001)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United Kingdom Patent Office (RO/GB)
0-7	Applicant's or agent's file reference	GPSBP5944723
I	Title of invention	CHROMATOGRAPHY METHODS AND CHROMATOGRAPHY APPARATUS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	EUROFLOW (UK) LIMITED
II-5	Address:	Brimscombe Port Business Park Brimscombe Stroud, Gloucestershire GL5 2QN United Kingdom
II-6	State of nationality	GB
II-7	State of residence	GB
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	HOFMANN, Martin,John
III-1-5	Address:	9 Whitehall Stroud, Gloucestershire GL5 1HA United Kingdom
III-1-6	State of nationality	GB
III-1-7	State of residence	GB

'CT REQUEST

GPSBP5944723

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IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	STONER, G., Patrick
IV-1-2	Address:	Mewburn Ellis York House 23 Kingsway London, Greater London WC2B 6HP United Kingdom
IV-1-3	Telephone No.	0117 926 6411
IV-1-4	Facsimile No.	020 7240 9339
IV-1-5	e-mail	patrick.stoner@mewburn.com
IV-2	**Additional agent(s)**	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	ARMITAGE, Ian, A.; BRASNETT, Adrian, H.; CALDERBANK, T., Roger; COLEIRO, Raymond; CRIPPS, Joanna, E.; DENISON, Christopher, M.; FORD, Michael, F.; HACKNEY, Nigel, J.; HARRISON, David, C.; KIDDLE, Simon, J.; KREMER, Simon, M.; LYONS, June, M.; NICHOLLS, Kathryn, M.; PAGET, Hugh, C.E.; SANDERSON, Michael, J.; STUART, Ian; WALTON, Sean, M.; WATSON, Robert, J.
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT

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GPSBP5944723

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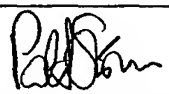
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	28 July 2000 (28.07.2000)
VI-1-2	Number	0018522.3
VI-1-3	Country	GB
VI-2	**Priority claim of earlier national application**	
VI-2-1	Filing date	14 May 2001 (14.05.2001)
VI-2-2	Number	0111785.2
VI-2-3	Country	GB
VI-3	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)

'CT REQUEST

GPSBP5944723

Original (for **SUBMISSION**) - printed on 30.07.2001 03:49:07 PM

VIII	Declarations	Number of declarations	
VIII-1	*Declaration as to the identity of the inventor*	–	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	–	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	–	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	–	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	–	
IX	**Check list**	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	–
IX-2	Description	36	–
IX-3	Claims	7	–
IX-4	Abstract	1	EZABST00.TXT
IX-5	*Drawings*	19	–
IX-7	TOTAL	68	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	–
IX-17	PCT-EASY diskette	–	Diskette
IX-18	Other (specified):	2 Form 23/77s	–
IX-19	**Figure of the drawings which should accompany the abstract**	13	
IX-20	**Language of filing of the international application**	English	
X-1	**Signature of applicant, agent or common representative**		
X-1-1	Name (LAST, First)	STONER, G., Patrick	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	***Date of timely receipt of the required corrections under PCT Article 11(2)***	
10-5	**International Searching Authority**	ISA/EP

'CT REQUEST

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10-6	Transmittal of search copy delayed until search fee is paid	

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11-1	Date of receipt of the record copy by the International Bureau	